SYNTHESIS OF 3-(ALKYL SULFANYL)-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-2H-1,4-benzothiazine-2-carbonitrile. Treatment with alkyl halides prior to workup yielded 3-(alkylsulfanyl)-4H-1,4-benzothiazine-2-carbonitriles. Successive treatment of these compounds with sodium hydride and alkyl halides afforded 4-alkyl-3-(alkylsulfanyl)-2H-1,4-benzothiazine-2-carbonitriles. These procedures can be applied to the synthesis of some 1,4-benzothiazine-based tricyclic heterocycles.

A number of 4H-1,4-benzothiazine derivatives have recently been synthesized and some of these compounds have been reported to exhibit biological activities.1 2H-1,4-Benzothiazine derivatives have also attracted respectable attention in recent years due to their potential use as biologically active compounds.2 Some 2H-3 and 4H-1,4-benzothiazine4 derivatives have been used for the preparation of more structurally complex organic compounds. The literature procedures to prepare 2H-1,4-benzothiazines usually involve the reactions of 2-aminobenzenethiol with α-halo ketones,5 though a few new syntheses of 2H-1,4-benzothiazine derivative have recently been reported.6 However, there have been no methods, which can allow preparation of 2H- or 4H-1,4-benzothiazine derivatives carrying an alkylsulfanyl group at the 3-position, while a few method for the preparation of 3,4-dihydro-2H-1,4-benzothiazine-3-thiones have been reported.2 In this manuscript, we wish to report a convenient and direct method for the preparation of 2-(alkylsulfanyl)-4H-1,4-benzothiazine (4) and 2-(alkylsulfanyl)-2H-
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 4\(b\) is somewhat lower (Entry 2) than the others.

![Scheme 1](image1.png)

**Scheme 1**

![Scheme 2](image2.png)

**Scheme 2**

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>RX</th>
<th>4</th>
<th>Yield/%(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeI</td>
<td>4(a)</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>(n)-BuBr</td>
<td>4(b)</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>CH(_2)=CHCH(_2)Br</td>
<td>4(c)</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>BnBr</td>
<td>4(d)</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>PhCOCH(_2)Br</td>
<td>4(e)</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>4-ClC(_6)H(_4)COCH(_2)Br</td>
<td>4(f)</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>(t)-BuOCOCH(_2)Br</td>
<td>4(g)</td>
<td>68</td>
</tr>
<tr>
<td>8</td>
<td>NCCH(_2)Br</td>
<td>4(h)</td>
<td>62</td>
</tr>
</tbody>
</table>

\(^a\)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\textit{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 \(\delta 156\) assignable to C(3) were observed in their \(^{13}\text{C}\) NMR spectra. The \(^1\text{H}\) NMR spectra were good agreement with their structures.

\[
\begin{align*}
\text{4a} & \quad R = \text{Me} \\
\text{4c} & \quad R = \text{allyl} \\
\text{4d} & \quad R = \text{Bn}
\end{align*}
\]

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,\textit{S}-dialkylation provided 2-alkyl-3-(alkylsulfanyl)-2\textit{H}-1,4-benzothiazines (6) directly in moderate yields, as shown in Scheme 4.

\[
\begin{align*}
\text{2} & \quad 1. \text{2 NaH, DMF, 0 °C} \\
& \quad 2. \text{2 RX, 0 °C}
\end{align*}
\]

Scheme 4

Compound 2 was then subjected to the treatment with two equivalents of sodium hydride in DMF at 0 °C, and an equimolar amount of 1,0-dibromoalkanes in place of two equivalents of alkyl halides were added. Surprisingly, however, it was found that the products obtained were 4,\textit{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,\textit{S}-dilakylated products. Synthesis and biological activities of...
thiazolo[2,3-c][1,4]benzothiazine derivatives ($n = 2$) have been reported.\textsuperscript{10}

![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.\textsuperscript{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\textsubscript{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-Isoncyanophenyl)sulfanyl]acetonitrile (1) was prepared according to the reported method.\textsuperscript{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.\textsuperscript{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 Et₃N (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 SiO₂ to give 2 (0.94 g, 85%); a yellow oil; Rf 0.32 (CH₂Cl₂/hexane 1:1); IR (neat) 2249, 2064 cm⁻¹; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 C₉H₆N₂S₂ (M): 205.9972. Found: m/z 205.9960.

3-Thioxo-3,4-dihydro-2H-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 NH₄Cl (15 mL) was added and the mixture was extracted with AcOEt (3 × 10 mL). The combined extracts were washed with H₂O (3 × 15 mL) and brine (10 mL), dried (Na₂SO₄), and concentrated by evaporation. The residual solid was recrystallized from hexane/CH₂Cl₂ to give 3 (0.13 g, 65%); an orange solid; mp 114–116 °C; IR (KBr) 3208, 2242, 1601, 1542, 1469 cm⁻¹; ¹H NMR (DMSO-d₆) 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); ¹³C NMR (DMSO-d₆) δ 37.03, 115.31, 117.73, 118.53, 125.71, 128.49, 128.60, 135.67, 182.15. HR-MS (EI). Calcd for C₉H₆N₂S₂: 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)-4H-1,4-benzothiazines (4). 3-(Methylsulfanyl)-4H-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/CH₂Cl₂ 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-d₆) δ 2.55 (s, 3H), 6.96 (d, J = 7.6 Hz, 1H), 7.05–7.10 (m, 2H), 7.19 (t, J = 7.4 Hz, 1H); ¹³C NMR (DMSO-d₆) 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 C₁₀H₈N₂S₂ (M): 220.0129. Found: m/z 220.0130. Anal. Calcd for C₁₀H₈N₂S₂: C, 54.52; H, 3.66; N, 12.72. Found: C, 54.31; H, 3.70; N, 12.59.

3-(Butylsulfanyl)-4H-1,4-benzothiazine-2-carbonitrile (4b): a yellow solid; mp 69–71 °C (hexane/CH₂Cl₂); IR (KBr) 3278, 2190, 1550, 1463 cm⁻¹; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 C₁₃H₁₄N₂S₂ (M): 262.0598. Found: m/z 262.0595.
3-[(Prop-2-enyl)sulfanyl]-4H-1,4-benzothiazine-2-carbonitride (4c): a yellow solid; mp 151–153 °C (hexane/THF); IR (KBr) 3321, 2183, 1635, 1541, 1463 cm⁻¹; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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). Caled for C₁₂H₁₀N₂S₂ (M): 246.0285. Found: m/z 246.0280. Anal. Caled for C₁₂H₁₀N₂S₂: C, 58.51; H, 4.09; N, 11.37. Found: C, 58.32; H, 4.05; N, 11.52.

3-[(Phenylmethyl)sulfanyl]-4H-1,4-benzothiazine-2-carbonitride (4d): a yellow solid; mp 100–103 °C (hexane/CH₂Cl₂); IR (KBr) 3258, 2191, 1550, 1466 cm⁻¹; ¹H NMR (DMSO-d₆) 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); ¹³C NMR (DMSO-d₆) 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). Caled for C₁₆H₁₂N₂S₂ (M): 296.0442. Found: m/z 296.0439. Anal. Caled for C₁₆H₁₂N₂S₂: 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]-4H-1,4-benzothiazine-2-carbonitride (4e): a yellow solid; mp 150–153 °C (hexane/CH₂Cl₂); IR (KBr) 3328, 2172, 1682 cm⁻¹; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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). Caled for C₁₇H₁₂N₂O₂S₂ (M): 324.0391. Found: m/z 324.0376. Anal. Caled for C₁₇H₁₂N₂O₂S₂: 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]-4H-1,4-benzothiazine-2-carbonitride (4f): a yellow solid; mp 154–156 °C (hexane/CH₂Cl₂); IR (KBr) 3337, 2173, 1678 cm⁻¹; ¹H NMR (DMSO-d₆) 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); ¹³C NMR (DMSO-d₆) 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). Caled for C₁₇H₁₂ClN₂O₂S₂ (M+H): 359.0079. Found: m/z 359.0066. Anal. Caled for C₁₇H₁₁ClN₂O₂S₂: 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-4H-1,4-benzothiazin-2-yl)sulfanyl]acetate (4g): a yellow viscous oil; Rf 0.34 (AcOEt/hexane 1:3); IR (neat) 3281, 2193, 1727 cm⁻¹; ¹H NMR (CDCl₃) 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 = 7.4 Hz, 1H), 8.93 (br s, 1H); ¹³C NMR (CDCl₃) 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). Caled for C₁₅H₁₆N₂O₂S₂ (M+H): 321.0731. Found: m/z 321.0725.
3-[(Cyanomethyl)sulfanyl]-4H-1,4-benzothiazine-2-carbonitrile (4h): a brown viscous oil; \( R_f \) 0.40 (AcOEt/hexane 1:4); IR (neat) 3288, 2194 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 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\(_3\)) \( \delta \) 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\(_7\)N\(_3\)S\(_2\) (M): 245.0081. Found: m/z 245.0073.

Typical Procedure for the Preparation of 2-Alkyl-3-(alkylsulfanyl)-2H-1,4-benzothiazine-2-carbonitriles (5).

2-Methyl-3-[(phenylmethyl)sulfanyl]-2H-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 \(^\circ\)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 \(^\circ\)C (hexane); IR (KBr) 2231, 1594 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 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\(_3\)) \( \delta \) 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\(_2\)S\(_2\) (M): 310.0598. Found: m/z 310.0607. Anal. Calcd for C\(_{17}\)H\(_{14}\)N\(_2\)S\(_2\): 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)-2H-1,4-benzothiazine-2-carbonitrile (5a): a white solid; mp 118–120 \(^\circ\)C (hexane/CH\(_2\)Cl\(_2\)); IR (KBr) 2227, 1593 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 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\(_3\)) \( \delta \) 14.24, 39.15, 44.23, 116.24, 117.62, 126.63, 126.78, 126.05, 128.20, 128.35, 130.45, 132.43, 141.25, 156.58. HR-MS (EI). Calcd for C\(_{17}\)H\(_{14}\)N\(_2\)S\(_2\) (M): 310.0598. Found: m/z 310.0589. Anal. Calcd for C\(_{17}\)H\(_{14}\)N\(_2\)S\(_2\): 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]-2H-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\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 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\(_3\)) \( \delta \) 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\(_2\)S\(_2\) (M+H): 261.0520. Found: m/z 261.0508.

Typical Procedure for the Preparation of 2-Alkyl-3-(alkylsulfanyl)-2H-1,4-benzothiazine-2-carbonitriles (6).

2-Methyl-3-(methylsulfanyl)-2H-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 \(^\circ\)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$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 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$_3$) $\delta$
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$_2$S$_2$: M) 234.0285. Found: m/z 234.0274. Anal. Calcd for C$_{11}$H$_{10}$N$_2$S$_2$: 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]-2H-1,4-benzothiazine-2-carbonitrile (6b): a pale-yellow oil;
$R_f$ 0.70 (AcOEt/hexane 1:3); IR (neat) 2239, 1639, 1593 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 2.53 (dd, $J = 13.5$, 7.4
Hz, 1H), 2.81 (ddd, $J = 13.5$, 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$_3$) $\delta$
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$_{13}$H$_{14}$N$_2$S$_2$: M) 286.0598. Found: m/z 286.0580.

2-(Phenylmethyl)-3-[(phenylmethyl)sulfanyl]-2H-1,4-benzothiazine-2-carbonitrile (6c): a pale-yellow solid; mp
100–102 °C (hexane); IR (KBr) 2241, 1596 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 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$_3$) $\delta$
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$_2$S$_2$: 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$_2$)$_2$Br (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$_2$Cl$_2$); IR (KBr) 2184, 1550 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 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$_3$) $\delta$
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$_6$N$_2$S$_2$: 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-1H-[1,4]benzothiazino[3,4-b]thiazine-5-carbonitrile (7b): a yellow solid; mp 117–119 °C
(hexane/CH$_2$Cl$_2$); IR (KBr) 2185, 1534 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 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$_3$) $\delta$
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_{2}S_{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_{2}Cl_{2}); IR (KBr) 2187, 1527 cm^{-1}; \textsuperscript{1}H NMR (CDCl_{3}) \delta 1.94–1.97 (m, 4H), 2.72–2.75 (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); \textsuperscript{13}C NMR (CDCl_{3}) \delta 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_{2}S_{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-9H-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}; \textsuperscript{1}H NMR (DMSO-d_{6}) \delta 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); \textsuperscript{13}C NMR (500 MHz, CDCl_{3}) \delta 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 (El). Calcd for C_{11}H_{7}N_{3}S_{2} (M): 245.0081. Found: m/z 245.0088. Anal. Calcd for C_{11}H_{7}N_{3}S_{2}: C, 53.85; H, 2.88; N, 17.13. Found:  C, 53.70; H, 3.16; N, 16.75.

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REFERENCES AND NOTES


