A New Synthesis of 4*H*-1,4-Benzothiazine Derivatives Based on Ring Closure of EWG-Stabilized (2-Isocyanophenylthio)methyl Anions

Kazuhiro Kobayashi,* Kazutaka Hayashi, Daisuke Iitsuka, Osamu Morikawa, Hisatoshi Konishi

Department of Materials Science, Faculty of Engineering, Tottori University, Koyama-minami, Tottori 680-8552, Japan
Fax +81(857)315263; E-mail: kkoba@chem.tottori-u.ac.jp

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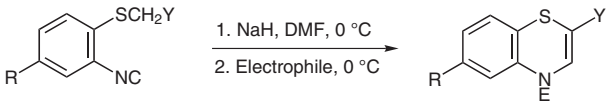
Abstract: 2-Cyano(phenylsulfinyl-, *p*-nitrophenyl-, or *o*-nitrophenyl-)methylthiophenyl isocyanides were synthesized from 2-aminobenzenethiols and were shown to undergo ring closure to 2,4-disubstituted 4*H*-1,4-benzothiazine derivatives by deprotonation of the hydrogen adjacent to the sulfur atom with sodium hydride or potassium *tert*-butoxide, followed by trapping with various electrophiles.

Key words: benzothiazine, carbanion, heterocycle, isocyanide, ring closure



1a R = H, Y = CN
1b R = CF_3, Y = CN
1c R = H, Y = S(O)Ph
1d R = H, Y = *p*-$O_2NC_6H_4$

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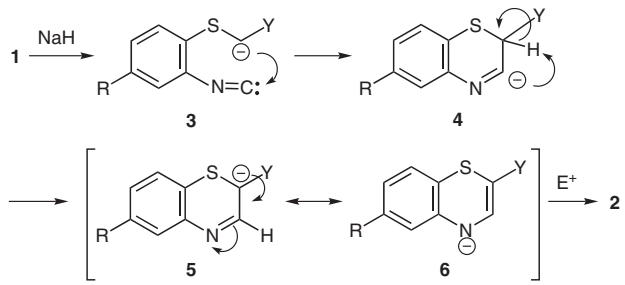
Scheme 1

4*H*-1,4-Benzothiazine derivatives are potentially of biological usefulness,[1] and some of their preparation[2] have been accomplished by starting from 2-aminobenzenethiol derivatives. For example, Gupta et al. reported that benzyl 3-methyl-4*H*-1,4-benzothiazine-2-carboxylates could be prepared by reactions of 2-aminobenzenethiols with benzyl 3-oxobutanoate.[2b] In this paper, we wish to report on a new method for constructing the 4*H*-1,4-benzothiazine system. The method is based on a deprotonation–ring-closure process of 2-cyano(phenylsulfinyl-, *p*-nitrophenyl-, or *o*-nitrophenyl-)methylthiophenyl isocyanides, which are easily prepared from 2-aminobenzenethiols, with an appropriate base.

We first attempted the transformation of (2-isocyanophenylthio)acetonitrile (**1a**) into 4*H*-1,4-benzothiazine-2-carbonitrile (**2a**, E = H). Thus, the ring closure of **1a** could be accomplished simply by treating it with sodium hydride in DMF at 0 °C, followed by quenching with aqueous acid, to give **2a** in good yield, as shown in Scheme 1 and Table 1 (entry 1). This reaction proved to furnish a range of 4-substituted derivatives **2b**–**m** in acceptable yields by treating various electrophiles before aqueous workup (entries 2–13). It was shown that a similar sequence using (2-isocyano-4-trifluoromethylphenyl)thioacetonitrile (**1b**) was also uneventfully carried out to afford the corresponding 4*H*-1,4-benzothiazine-2-carbonitriles **2n** and **2o** in fair yields (entries 14 and 15). We also found that 1-isocyano-2-(phenylsulfinylmethylthio)benzene (**1c**) and 1-isocyano-2-(4-nitrophenylmethylthio)benzene (**1d**) also underwent transformation into the corresponding 4*H*-1,4-benzothiazine derivatives **2p**–**t** in moderate to fair yields on treatment with sodium hydride and suitable electrophiles (entries 17–21). It should be noted that 2-phenylsulfinyl-4*H*-1,4-benzothiazine was too unstable to be isolated in pure form (entry 16), though we cannot explain the reason for its instability.

The probable pathway to 4*H*-1,4-benzothiazine derivatives **2** is illustrated in Scheme 2. Thus, the deprotonation of the hydrogen adjacent to the sulfur atom with sodium hydride generates the carbanion intermediate **3**. This carbanion attacks intramolecularly on the isocyano carbon to give the imidoyl anion intermediate **4**, which undergoes intra- or intermolecular proton migration to result in formation of the stabilized carbanion **5**. Its resonance form **6** is trapped with an electrophile to give **2**.



Scheme 2

Similar treatment of 1-isocyano-2-(2-nitrophenylmethyl)thiobenzene (**7**) with sodium hydride proved to result in the formation of an intractable mixture of products, but potassium *tert*-butoxide effected the deprotonation–ring-closure sequence and furnished 2-(2-nitrophenyl)-4*H*-1,4-benzothiazine (**8**) in moderate yield, as shown in Scheme 3.

It is concluded from the results described that a facile synthetic method of 4*H*-1,4-benzothiazine derivatives in four steps from commercially available 2-aminobenzenethiols, via intermediate isocyano compounds, has been developed. This method has advantages over previously report-

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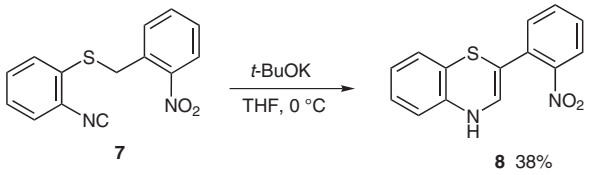
Table 1 Synthesis of 4*H*-1,4-Benzothiazine Derivatives **2**

Entry	Isocyanide **1**	Electrophile	E in **2**	Product	Yield (%)[a]
1	**1a**	H_2O	H	**2a**	85
2	**1a**	MeI	Me	**2b**	61
3	**1a**	CH_2=$CHCH_2Br$	Allyl	**2c**	65
4	**1a**	BnBr	Bn	**2d**	68
5	**1a**	2-$CNC_6H_4CH_2Br$	2-$CNC_6H_4CH_2$	**2e**	50
6	**1a**	4-$CNC_6H_4CH_2Br$	4-$CNC_6H_4CH_2$	**2f**	58
7	**1a**	4-$CO_2MeC_6H_4CH_2Br$	4-$CO_2MeC_6H_4CH_2$	**2g**	70
8	**1a**	$BrCH_2CO_2Me$	CH_2CO_2Me	**2h**	77
9	**1a**	EtCOCl	COEt	**2i**	58
10	**1a**	MeOCOCl	CO_2Me	**2j**	72
11	**1a**	$(Boc)_2O$	CO_2t-Bu	**2k**	64
12	**1a**	PhNCO	CONHPh	**2l**	31
13	**1a**	TsCl	Ts	**2m**	47
14	**1b**	H_2O	H	**2n**	70
15	**1b**	MeI	Me	**2o**	68
16	**1c**	H_2O	H	–[b]	–[b]
17	**1c**	MeI	Me	**2p**	68
18	**1c**	$BrCH_2CN$	CH_2CN	**2q**	58
19	**1c**	PhCOCl	COPh	**2r**	60
20	**1d**	H_2O	H	**2s**	42
21	**1d**	MeI	Me	**2t**	46

[a] Isolated yields.
[b] The corresponding product was too unstable to be isolated.



Scheme 3

ed methods,[2] because it makes possible the synthesis of 4*H*-1,4-benzothiazine derivatives bearing a variety of functional groups from readily available starting materials by simple operations. We are presently attempting to extend the present ring-closure process to the synthesis of related heterocycles.

Melting points were determined on a Laboratory Devices MEL-TEMP II melting-point apparatus and are uncorrected. The IR spectra were recorded on a Shimadzu FTIR-8300 spectrometer. The ^1H NMR spectra were determined using $SiMe_4$ as an internal reference in $CDCl_3$ with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz or a JEOL LA400 FT NMR spectrometer operating at 400 MHz. Low-resolution mass spectra were recorded on a JEOL AUTOMASS 20 spectrometer (Center for Joint Research and Development, this University). Thin-layer chromatography (TLC) was carried out on Merck Kieselgel 60 PF_{254}. All of the solvents used were dried over appropriate drying agents and distilled under argon prior to use. All of the reactions were carried out under argon.

(2-Aminophenylthio)acetonitrile[3] and chloromethyl phenyl sufoxide[4] were prepared by appropriate reported procedures. All other chemicals used in this study were commercially available.

2-[(Formylamino)phenylthio]acetonitrile

A solution of (2-aminophenylthio)acetonitrile[3] (2.2 g, 13 mmol) in toluene (13 mL) containing formic acid (3.1 g, 67 mmol) was refluxed under azeotropic conditions for 15 min. After cooling the solvent and excess formic acid were removed under reduced pressure to give a residue, which was purified by column chromatography on silica gel (1:1 hexane–THF) to afford the title compound (2.1 g, 83%); pale-yellow solid; mp 77–78 °C (hexane–Et_2O).

IR (KBr): 3317, 2245, 1693 cm^{-1}.

^1H NMR (500 MHz): δ = 3.46 (2 H, s), 7.16–7.76 (4 H, m), 8.21–8.83 (2 H, m).

Anal. Calcd for $C_9H_8N_2OS$: C, 56.23; H, 4.19; N, 14.57; S, 16.68. Found: C, 56.09; H, 4.20; N, 14.50; S, 16.80.

2-(Isocyanophenylthio)acetonitrile (1a)
To a stirred solution of [2-(formylamino)phenylthio]acetonitrile (0.49 g, 2.6 mmol) in THF (4 mL) containing Et_3N (1.8 g, 18 mmol) at 0 °C was added $POCl_3$ (0.39 g, 2.6 mmol) dropwise. After 5 min, sat. aq $NaHCO_3$ (20 mL) was added and the mixture was extracted with Et_2O (3 × 15 mL). The combined extracts were washed with sat. aq $NaHCO_3$ and brine, dried (K_2CO_3), and evaporated. The residue was subjected to purification by column chromatography on silica gel (2:1 hexane–THF) to give **1a** (0.32 g, 71%); yellow solid; mp 62–63 °C (hexane–Et_2O).

IR (KBr): 2247, 2122 cm^{-1}.

^1H NMR (500 MHz): δ = 3.72 (2 H, s), 7.43–7.51 (3 H, m), 7.69 (1 H, dd, *J* = 8.2, 1.4 Hz).

MS: *m*/*z* (%) = 174 (100, $[M^+]$).

Anal. Calcd for $C_9H_6N_2S$: C, 62.04; H, 3.47; N, 16.08; S, 18.41. Found: C, 62.14; H, 3.51; N, 15.98; S, 18.28.

(2-Amino-4-trifluoromethylphenylthio)acetonitrile
This compound was prepared from 2-amino-4-trifluoromethylbenzenethiol and bromoacetonitrile according to the procedure previously reported for the preparation of 2-(aminophenylthio)acetonitrile;[3] yield: 88%; pale-yellow oil; R_f = 0.21 (1:2 THF–hexane).

IR (neat): 3470, 3368, 2247, 1622 cm^{-1}.

^1H NMR (400 MHz): δ = 3.48 (2 H, s), 4.59 (2 H, br s), 6.97–6.70 (2 H, m), 7.62 (1 H, d, *J* = 7.7 Hz).

Anal. Calcd for $C_9H_7F_3N_2S$: C, 46.55; H, 3.04; N, 12.06; S, 13.81. Found: C, 46.43; H, 3.12; N, 12.05; S, 13.77.

(2-Formylamino-4-trifluoromethylphenylthio)acetonitrile
This compound was prepared from (2-amino-4-trifluoromethylphenylthio)acetonitrile as described for the preparation of [2-(formylamino)phenylthio]acetonitrile; yield 80%; pale-yellow solid; mp 95–96 °C (hexane–Et_2O).

IR (KBr): 3283, 2253, 1695 cm^{-1}.

^1H NMR (500 MHz): δ = 3.52 and 3.54 (combined 2 H, 2 s), 7.37–7.58 (1 H, m), 7.81–7.87 (1 H, m), 8.19–8.84 (3 H, m).

Anal. Calcd for $C_{10}H_7F_3N_2OS$: C, 46.15; H, 2.71; N, 10.76; S, 12.32. Found: C, 46.04; H, 2.82; N, 10.54; S, 12.29.

(2-Isocyano-4-trifluoromethylphenylthio)acetonitrile (1b)
This compound was prepared from (2-formylamino-4-trifluoromethylphenylthio)acetonitrile as described for the preparation of **1a**; yield: 64%; pale-yellow solid; mp 59–62 °C (hexane–Et_2O).

IR (KBr): 2251, 2124, 1612 cm^{-1}.

^1H NMR (500 MHz): δ = 3.80 (2 H, s), 7.70–7.74 (3 H, m).

Anal. Calcd for $C_{10}H_5F_3N_2S$: C, 49.59; H, 2.08; N, 11.57; S, 13.24. Found: C, 49.46; H, 2.11; N, 11.36; S, 13.22.

2-(Phenylsulfinylmethylthio)benzenamine
This compound was prepared from 2-aminobenzenethiol and chloromethyl phenyl sufoxide[4] according to the procedure previously reported for the preparation of 2-(aminophenylthio)acetonitrile;[3] yield: 97%; pale-yellow solid; mp 96–100 °C (hexane–Et_2O–CH_2Cl_2).

IR (KBr): 3441, 3327, 1614, 1043 cm^{-1}.

^1H NMR (500 MHz): δ = 3.97 (1 H, d, *J* = 13.3 Hz), 3.99 (1 H, d, *J* = 13.3 Hz), 4.57 (2 H, br s), 6.66 (1 H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 6.73 (1 H, dd, *J* = 7.8, 1.4 Hz), 7.16 (1 H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.39 (1 H, dd, *J* = 7.8, 1.4 Hz), 7.49–7.54 (3 H, m), 7.65–7.69 (2 H, m).

Anal. Calcd for $C_{13}H_{13}NOS_2$: C, 59.28; H, 4.98; N, 5.32; S, 24.35. Found: C, 59.18; H, 5.01; N, 5.37; S, 24.19.

***N*-[2-(Phenylsulfinylmethylthio)phenyl]formamide**
This compound was prepared from 2-(phenylsulfinylmethylthio)benzeneamine as described for the preparation of [2-(formylamino)phenylthio]acetonitrile; yield: 99%; pale-yellow viscous oil; R_f = 0.18 (1:1 EtOAc–hexane).

IR (neat): 3244, 1693, 1084 cm^{-1}.

^1H NMR (500 MHz): δ = 4.02 (1 H, d, *J* = 13.7 Hz), 4.12 (1 H, d, *J* = 13.7 Hz), 7.03–7.66 (9 H, m), 8.36–9.83 (2 H, m).

Anal. Calcd for $C_{14}H_{13}NO_2S_2$: C, 57.71; H, 4.50; N, 4.81; S, 22.01. Found: C, 57.65; H, 4.51; N, 4.64; S, 22.22.

1-Isocyano-2-(phenylsufinylmethylthio)benzene (1c)
This compound was prepared from *N*-[2-(phenylsulfinylmethylthio)phenyl]formamide as described for the preparation of **1a**; yield: 71%; pale-yellow solid; mp 51–53 °C (hexane–Et_2O).

IR (KBr): 2120, 1047 cm^{-1}.

^1H NMR (500 MHz): δ = 4.20 (1 H, d, *J* = 13.7 Hz), 4.22 (1 H, d, *J* = 13.7 Hz), 7.31 (1 H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.37 (1 H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.39 (1 H, dd, *J* = 7.8, 1.4 Hz), 7.51–7.54 (3 H, m), 7.64 (1 H, dd, *J* = 7.8, 1.4 Hz), 7.70–7.73 (2 H, m).

Anal. Calcd for $C_{14}H_{11}NOS_2$: C, 61.51; H, 4.06; N, 5.12; S, 23.46. Found: C, 61.46; H, 4.09; N, 5.11; S, 23.46.

2-(4-Nitrophenylmethylthio)benzenamine
This compound was prepared from 2-aminobenzenethiol and 1-bromomethyl-4-nitrobenzene according to the procedure previously reported for the preparation of 2-(aminophenylthio)acetonitrile;[3] yield: 70%; yellow solid; mp 58–60 °C (hexane–Et_2O).

IR (KBr): 1618, 1512, 1342 cm^{-1}.

^1H NMR (500 MHz): δ = 3.93 (2 H, s), 4.27 (2 H, br s), 6.58 (1 H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 6.71 (1 H, dd, *J* = 7.8, 1.4 Hz), 7.07 (1 H, dd, *J* = 7.8, 1.4 Hz), 7.12 (1 H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.21 (2 H, d, *J* = 8.7 Hz), 8.07 (2 H, d, *J* = 8.7 Hz).

Anal. Calcd for $C_{13}H_{12}N_2O_2S$: C, 59.98; H, 4.65; N, 10.76; S, 12.32. Found: C, 59.77; H, 4.62; N, 10.76; S, 12.32.

***N*-[2-(4-Nitrophenylmethylthio)phenyl]formamide**
This compound was prepared from 2-(4-nitrophenylmethylthio)benzenamine as described for the preparation of [2-(formylamino)phenylthio]acetonitrile; yield: 81%; white solid; mp 119–121 °C (hexane–Et_2O–CH_2Cl_2).

IR (KBr): 3234, 1666, 1515, 1342 cm^{-1}.

^1H NMR (500 MHz): δ = 3.94 and 3.95 (combined 3 H, 2 s), 6.99–7.39 (5 H, m), 8.09 (2 H, d, *J* = 8.7 Hz), 8.24–8.68 (2 H, m).

Anal. Calcd for $C_{14}H_{12}N_2O_3S$: C, 58.32; H, 4.20; N, 9.72; S, 11.12. Found: C, 58.30; H, 4.44; N, 9.69; S, 11.09.

1-Isocyano-2-(4-nitrophenylmethylthio)benzene (1d)
This compound was prepared from *N*-[2-(4-nitrophenylmethylthio)phenyl]formamide as described for the preparation of **1a**; yield 74%; pale-yellow solid; mp 110–113 °C (hexane).

IR (KBr): 2120, 1607, 1520, 1346 cm^{-1}.

^{1}H NMR (500 MHz): δ = 4.23 (2 H, s), 7.26–7.41 (4 H, m), 7.44 (2 H, d, *J* = 8.7 Hz), 8.14 (2 H, d, *J* = 8.7 Hz).

Anal. Calcd for $C_{14}H_{10}N_2O_2S$: C, 62.21; H, 3.73; N, 10.36; S, 11.86. Found: C, 62.24; H, 3.76; N, 10.46; S, 11.78.

4*H*-1,4-Benzothiazine-2-carbonitrile (2a)
To a stirred suspension of NaH (29 mg, 60% in oil, 0.72 mmol) in DMF (2 mL) at 0 °C was added a solution of **1a** (0.13 g, 0.72 mmol) in DMF (1.5 mL) dropwise. After 5 min, sat. aq NH_4Cl (10 mL) was added and the mixture was extracted with Et_2O (3 × 10 mL). The combined extracts were washed with H_2O (2 ×) and brine (1 ×), dried (Na_2SO_4), and evaporated. The residue was purified by preparative TLC on silica gel (2:1 hexane–THF) to give **2a** (0.11 g, 85%); brownish-yellow solid; mp 119–120 °C (hexane–Et_2O).

IR (KBr): 3282, 2193, 1628 cm^{-1}.

^{1}H NMR (500 MHz): δ = 5.96 (1 H, br s), 6.41 (1 H, dd, *J* = 7.8, 1.4 Hz), 6.80 (1 H, d, *J* = 6.9 Hz), 6.82 (1 H, dd, *J* = 7.8, 1.4 Hz), 6.91 (1 H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 6.99 (1 H, ddd, *J* = 7.8, 7.3, 1.4 Hz).

MS: *m*/*z* (%) = 174 (100, [M$^+$]).

Anal. Calcd for $C_9H_6N_2S$: C, 62.04; H, 3.47; N, 16.08; S, 18.41. Found: C, 62.03; H, 3.40; N, 15.98; S, 18.33.

4-Substituted 4*H*-1,4-Benzothiazine Derivatives; 4-Methyl-4*H*-1,4-benzothiazine-2-carbonitrile (2b); Typical Procedure
After treatment of **1a** (0.22 g, 1.3 mmol) with NaH (61 mg, 60% in oil, 1.5 mmol) in a manner similar to that described above for the preparation of **2a**, MeI (0.22 g, 1.5 mmol) was added and stirring was continued for 30 min. Similar workup of the resulting mixture was followed by purification by preparative TLC on silica gel (3:1 hexane–THF) to give **2b** (0.15 g, 61%); yellow solid; mp 72–73 °C (hexane–Et_2O).

IR (KBr): 2201, 1626 cm^{-1}.

^{1}H NMR (500 MHz): δ = 3.16 (3 H, s), 6.65 (1 H, dd, *J* = 7.8, 0.9 Hz), 6.74 (1 H, s), 6.88 (1 H, dd, *J* = 7.8, 1.4 Hz), 6.96 (1 H, dd, *J* = 7.8, 7.3, 0.9 Hz), 7.09 (1 H, ddd, *J* = 7.8, 7.3, 1.4 Hz).

MS: *m*/*z* (%) = 188 (100, [M$^+$]).

Anal. Calcd for $C_{10}H_8N_2S$: C, 63.80; H, 4.28; N, 14.88; S, 17.03. Found: C, 63.72; H, 4.24; N, 14.76; S, 17.16.

4-Allyl-4*H*-1,4-benzothiazine-2-carbonitrile (2c)
Yield: 65%; brownish-yellow oil; R_f = 0.35 (1:5 EtOAc–hexane).

IR (neat): 2197, 1622 cm^{-1}.

^{1}H NMR (500 MHz): δ = 4.10–4.12 (2 H, m), 5.33–5.38 (2 H, m), 5.84–5.92 (1 H, m), 6.65 (1 H, dd, *J* = 8.2, 0.9 Hz), 6.79 (1 H, s), 6.89 (1 H, dd, *J* = 7.8, 1.4 Hz), 6.95 (1 H, ddd, *J* = 7.8, 7.3, 0.9 Hz), 7.62 (1 H, ddd, *J* = 8.2, 7.3, 1.4 Hz).

MS; *m*/*z* (%) = 214 (13, [M$^+$]), 173 (100).

Anal. Calcd for $C_{12}H_{10}N_2S$: C, 67.26; H, 4.70; N, 13.07; S, 14.96. Found: C, 67.18; H, 4.73; N, 12.99; S, 14.96.

4-Benzyl-4*H*-1,4-benzothiazine-2-carbonitrile (2d)
Yield: 68%; brownish-yellow viscous oil; R_f = 0.31 (1:5 EtOAc–hexane).

IR (neat): 2195, 1626 cm^{-1}.

^{1}H NMR (500 MHz): δ = 4.70 (2 H, s), 6.60 (1 H, dd, *J* = 7.8, 1.4 Hz), 6.80 (1 H, s), 6.90 (1 H, dd, *J* = 7.8, 1.8 Hz), 6.93 (1 H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 6.98 (1 H, ddd, *J* = 7.8, 7.3, 1.8 Hz), 7.30–7.34 (3 H, m), 7.40 (2 H, t, *J* = 7.3 Hz).

MS: *m*/*z* (%) = 264 (15, [M$^+$]), 92 (100).

Anal. Calcd for $C_{16}H_{12}N_2S$: C, 72.70; H, 4.58; N, 10.60; S, 12.13. Found: C, 72.58; H, 4.72; N, 10.71; S, 11.99.

4-(2-Cyanophenylmethyl)-4*H*-1,4-benzothiazine-2-carbonitrile (2e)
Yield: 50%; yellow solid; mp 135–136 °C (hexane–Et_2O).

IR (KBr): 2222, 2197, 1636 cm^{-1}.

^{1}H NMR (400 MHz): δ = 4.92 (2 H, s), 6.51 (1 H, dd, *J* = 8.1, 1.5 Hz), 6.80 (1 H, s), 6.91–7.03 (3 H, m), 7.46 (1 H, t, *J* = 7.7 Hz), 7.57 (1 H, d, *J* = 7.3 Hz), 7.64 (1 H, ddd, *J* = 8.1, 7.7, 1.1 Hz), 7.74 (1 H, dd, *J* = 7.7, 1.1 Hz).

MS: *m*/*z* (%) = 289 (32, [M$^+$]), 173 (100).

Anal. Calcd for $C_{17}H_{11}N_3S$: C, 70.56; H, 3.83; N, 14.52; S, 11.08. Found: C, 70.48; H, 3.69; N, 14.35; S, 11.14.

4-(4-Cyanophenylmethyl)-4*H*-1,4-benzothiazine-2-carbonitrile (2f)
Yield: 58%; yellow solid; mp 143–144 °C (hexane–Et_2O).

IR (KBr): 2222, 2199, 1630 cm^{-1}.

^{1}H NMR (400 MHz): δ = 4.77 (2 H, s), 6.45 (1 H, dd, *J* = 7.3, 2.4 Hz), 6.78 (1 H, s), 6.90–7.00 (3 H, m), 7.48 (2 H, d, *J* = 7.9 Hz), 7.69 (2 H, d, *J* = 7.9 Hz).

MS: *m*/*z* (%) = 289 (2.4, [M$^+$]), 173 (100).

Anal. Calcd for $C_{17}H_{11}N_3S$: C, 70.56; H, 3.83; N, 14.52; S, 11.08. Found: C, 70.53; H, 3.78; N, 14.26; S, 11.46.

4-(4-Methoxycarbonylphenylmethyl)-4*H*-1,4-benzothiazine-2-carbonitrile (2g)
Yield: 70%; yellow solid; mp 147–148 °C (hexane–Et_2O).

IR (KBr): 2195, 1707, 1628 cm^{-1}.

^{1}H NMR (400 MHz): δ = 3.92 (3 H, s), 4.75 (2 H, s), 6.50 (1 H, dd, *J* = 7.3, 1.8 Hz), 6.79 (1 H, s), 6.88–6.98 (3 H, m), 7.41 (2 H, d, *J* = 8.0 Hz), 8.06 (2 H, d, *J* = 8.0 Hz).

MS: *m*/*z* (%) = 322 (21, [M$^+$]), 173 (100).

Anal. Calcd for $C_{18}H_{14}N_2O_2S$: C, 67.06; H, 4.38; N, 8.69; S, 9.95. Found: C, 66.77; H, 4.38; N, 8.62; S, 9.92.

4-Methoxycarbonylmethyl-4*H*-1,4-benzothiazine-2-carbonitrile (2h)
Yield: 77%; yellow solid; mp 118–119 °C (hexane–Et_2O).

IR (KBr): 2195, 1738, 1634 cm^{-1}.

^{1}H NMR (400MHz): δ = 3.82 (3 H, s), 4.18 (2 H, s), 6.43 (1 H, d, *J* = 8.4 Hz), 6.78 (1 H, s), 6.92 (1 H, dd, *J* = 7.8, 1.5 Hz), 6.97 (1 H, ddd, *J* = 7.8, 7.3, 1.1 Hz), 7.06 (1 H, ddd, *J* = 8.4, 7.3, 1.5 Hz).

MS: *m*/*z* (%) = 246 (44, [M$^+$]), 187 (100).

Anal. Calcd for $C_{12}H_{10}N_2O_2S$: C, 58.52; H, 4.09; N, 11.37; S, 13.02. Found: C, 58.44; H, 4.01; N, 11.25; S, 12.89.

4-Propanoyl-4*H*-1,4-benzothiazine-2-carbonitrile (2i)
Yield: 58%; pale-yellow solid; mp 89–90 °C (hexane–Et_2O).

IR (KBr): 2230, 1703, 1607 cm^{-1}.

^{1}H NMR (500 MHz): δ = 1.26 (3 H, t, *J* = 7.3 Hz), 2.63 (2 H, q, *J* = 7.3 Hz), 7.25–7.28 (2 H, m), 7.34 (1 H, ddd, 7.8, 7.3, 1.8 Hz), 7.42 (1 H, d, *J* = 8.2 Hz), 7.65 (1 H, s).

MS: *m*/*z* (%) = 230 (8.5, [M$^+$]), 174 (100).

Anal. Calcd for $C_{12}H_{10}N_2OS$: C, 62.59; H, 4.38; N, 12.16; S, 13.92. Found: C, 62.55; H, 4.30; N, 12.10; S, 14.03.

4-Methoxycarbonyl-4*H*-1,4-benzothiazine-2-carbonitrile (2j)
Yield: 72%; yellow solid; mp 94–95 °C (hexane–Et_2O).

IR (KBr): 2230, 1744, 1624 cm^{-1}.

^{1}H NMR (500 MHz): δ = 3.95 (3 H, s), 7.18 (1 H, dd, *J* = 7.8, 1.8 Hz), 7.21 (1 H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.31 (1 H, ddd, *J* = 7.8, 7.3, 1.8 Hz), 7.57 (1 H, s), 7.60 (1 H, dd, *J* = 7.8, 1.4 Hz).

MS: *m*/*z* (%) = 232 (70, [M$^+$]), 173 (100).

Anal. Calcd for $C_{11}H_8N_2O_2S$: C, 56.88; H, 3.47; N, 12.06; S, 13.81. Found: C, 56.91; H, 3.50; N, 12.02; S, 14.05.

4-*tert*-Butoxycarbonyl-4*H*-1,4-benzothiazine-2-carbonitrile (2k)
Yield: 64%; white solid; mp 122 °C (hexane–Et_2O).

IR (KBr): 2232, 2218, 1738, 1614 cm^{-1}.

^{1}H NMR (500 MHz): δ = 1.59 (9 H, s), 7.16 (1 H, dd, *J* = 7.8, 1.8 Hz), 7.18 (1 H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.28 (1 H, ddd, *J* = 7.8, 7.3, 1.8 Hz), 7.54 (1 H, s), 7.59 (1 H, d, *J* = 7.8 Hz).

MS: *m*/*z* (%) = 274 (0.44, [M$^+$]), 174 (100).

Anal. Calcd for $C_{14}H_{14}N_2O_2S$: C, 61.29; H, 5.14; N, 10.21; S, 11.69. Found: C, 61.24; H, 5.14; N, 10.18; S, 11.75.

4-Phenylaminocarbonyl-4*H*-1,4-benzothiazine-2-carbonitrile (2l)
Yield: 31%; yellow solid; mp 124–125 °C (hexane–Et_2O).

IR (KBr): 3304, 2220, 1697, 1601 cm^{-1}.

^{1}H NMR (500 MHz): δ = 7.11 (1 H, br s), 7.17 (1 H, t, *J* = 7.3 Hz), 7.27–7.32 (2 H, m), 7.33–7.39 (4 H, m), 7.43 (2 H, d, *J* = 8.2 Hz), 7.97 (1 H, s).

MS: *m*/*z* (%) = 293 (2.2, [M$^+$]), 216 (31), 173 (100).

Anal. Calcd for $C_{16}H_{11}N_3OS$: C, 65.51; H, 3.78; N, 14.32; S, 10.93. Found: C, 65.58; H, 3.78; N, 14.19; S, 11.08.

4-(4-Methylphenylsulfonyl)-4*H*-1,4-benzothiazine-2-carbonitrile (2m)
Yield: 47%; yellow solid; mp 122–122.5 °C (hexane–Et_2O).

IR (KBr): 2214, 1602, 1373, 1175 cm^{-1}.

^{1}H NMR (500 MHz): δ = 2.43 (3 H, s), 6.99 (1 H, dd, *J* = 7.8, 1.4 Hz), 7.23 (1 H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.25 (2 H, d, *J* = 8.7 Hz), 7.33 (1 H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.36 (1 H, s), 7.57 (2 H, dd, *J* = 8.7 Hz), 7.70 (1 H, dd, *J* = 7.8, 1.4 Hz).

MS: *m*/*z* (%) = 328 (8.6, [M$^+$]), 278 (23), 173 (100).

Anal. Calcd for $C_{16}H_{12}N_2O_2S_2$: C, 58.52; H, 3.68; N, 8.53; S, 19.53. Found: C, 58.49; H, 3.66; N, 8.50; S, 19.79.

6-Trifluoromethyl-4*H*-1,4-benzothiazine-2-carbonitrile (2n)
Prepared from **1b** as described for the preparation of **2a**; yield 70%; yellow solid; mp 97–99 °C (hexane–Et_2O).

IR (KBr): 3279, 2199, 1634 cm^{-1}.

^{1}H NMR (500 MHz): δ = 6.23 (1 H, br s), 6.61 (1 H, d, *J* = 1.4 Hz), 6.76 (1 H, d, *J* = 6.4 Hz), 6.89 (1 H, d, *J* = 7.8 Hz), 7.12 (1 H, dd, *J* = 7.8, 1.4 Hz).

MS: *m*/*z* (%) = 242 (100, [M$^+$]).

Anal. Calcd for $C_{10}H_5F_3N_2S$: C, 49.59; H, 2.08; N, 11.57; S, 13.24. Found: C, 49.29; H, 2.08; N, 11.66; S, 13.17.

4-Methyl-6-trifluoromethyl-4*H*-1,4-benzothiazine-2-carbonitrile (2o)
Yield: 68%; yellow solid; mp 134–135 °C (hexane–Et_2O).

IR (KBr): 2197, 1634 cm^{-1}.

^{1}H NMR (400 MHz): δ = 3.17 (3 H, s), 6.71 (1 H, s), 6.76 (1 H, s), 6.94 (1 H, d, *J* = 8.1 Hz), 7.19 (1 H, d, *J* = 8.1 Hz).

MS: *m*/*z* (%) = 256 (100, [M$^+$]).

Anal. Calcd for $C_{11}H_7F_3N_2S$: C, 51.56; H, 2.75; N, 10.93; S, 12.51. Found: C, 51.48; H, 2.95; N, 10.71; S, 12.49.

4-Methyl-2-phenylsulfinyl-4*H*-1,4-benzothiazine (2p)
Yield: 68%; yellow solid; mp 139–141 °C (Et_2O–CH_2Cl_2).

IR (KBr): 1622, 1040 cm^{-1}.

^{1}H NMR (500 MHz): δ = 3.18 (3 H, s), 6.59 (1 H, dd, *J* = 8.2, 0.9 Hz), 6.75 (1 H, dd, *J* = 7.8, 1.4 Hz), 6.82 (1 H, ddd, *J* = 7.8, 7.3, 0.9 Hz), 6.96 (1 H, s), 7.00 (1 H, ddd, *J* = 8.2, 7.3, 1.4 Hz), 7.46–7.54 (3 H, m), 7.67 (2 H, dd, *J* = 8.2, 1.4 Hz).

MS: *m*/*z* (%) = 287 (0.44, [M$^+$]), 162 (100).

Anal. Calcd for $C_{15}H_{13}NOS_2$: C, 62.69; H, 4.56; N, 4.87; S, 22.31. Found: C, 62.59; H, 4.56; N, 4.79; S, 22.30.

(2-Phenylsulfinyl-4*H*-1,4-benzothiazin-4-yl)acetonitrile (2q)
Yield: 58%; yellow solid; mp 122–124 °C (hexane–Et_2O–CH_2Cl_2).

IR (KBr): 2210, 1626, 1040 cm^{-1}.

^{1}H NMR (500 MHz): δ = 4.39 (2 H, s), 6.72 (1 H, d, *J* = 8.2 Hz), 6.86 (1 H, d, *J* = 7.8, 1.4 Hz), 6.93 (1 H, ddd, *J* = 7.8, 7.3, 0.9 Hz), 7.02 (1 H, s), 7.12 (1 H, *J* = 8.2, 7.3, 1.4 Hz), 7.50–7.56 (3 H, m), 7.69 (2 H, dd, 7.8, 1.4 Hz).

MS: *m*/*z* (%) = 312 (100, [M$^+$]).

Anal. Calcd for $C_{16}H_{12}N_2OS_2$: C, 61.51; H, 3.87; N, 8.97; S, 20.53. Found: C, 61.42; H, 3.86; N, 9.22; S, 20.53.

4-Benzoyl-2-phenylsulfinyl-4*H*-1,4-benzothiazine (2r)
Yield: 60%; pale-yellow solid; mp 148–150 °C (CH_2Cl_2).

IR (KBr): 1668, 1612, 1051 cm^{-1}.

^{1}H NMR (500 MHz): δ = 6.78 (1 H, d, *J* = 7.8 Hz), 6.96 (1 H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.06 (1 H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.19 (1 H, dd, *J* = 7.8, 1.4 Hz), 7.35 (2 H, dd, *J* = 8.2, 7.8 Hz), 7.47 (1 H, tt, *J* = 7.8, 1.4 Hz), 7.54–7.58 (5 H, m), 7.72 (2 H, dd, *J* = 8.2, 1.4 Hz), 8.12 (1 H, s).

MS: *m*/*z* (%) = 377 (5.6, [M$^+$]), 256 (100).

Anal. Calcd for $C_{21}H_{15}NO_2S_2$: C, 66.82; H, 4.01; N, 3.71; S, 16.99. Found: C, 66.71; H, 3.97; N, 3.46; S, 16.96.

2-(4-Nitrophenyl)-4*H*-1,4-benzothiazine (2s)
Prepared from **1d** as described for the preparation of **2a**; yield: 42%; dark-red solid; mp 145–147 °C (hexane–Et_2O).

IR (KBr): 3387, 1634, 1568, 1329 cm^{-1}.

^{1}H NMR (500 MHz): δ = 5.66 (1 H, br d, *J* = 5.5 Hz), 6.45 (1 H, d, *J* = 6.9 Hz), 6.81 (1 H, d, *J* = 6.4 Hz), 6.87 (1 H, dd, *J* = 7.3, 6.9 Hz), 6.95 (1 H, d, *J* = 7.3 Hz), 6.98 (1 H, t, *J* = 7.3 Hz), 7.51 (2 H, d, *J* = 8.7 Hz), 8.15 (2 H, d, *J* = 8.7 Hz).

MS: *m*/*z* (%) = 270 (100, [M$^+$]).

Anal. Calcd for $C_{14}H_{10}N_2O_2S$: C, 62.21; H, 3.73; N, 10.36; S, 11.86. Found: C, 62.21; H, 3.92; N, 10.24; S, 11.63.

4-Methyl-2-(4-nitrophenyl)-4*H*-1,4-benzothiazine (2t)
Yield: 46%; dark-red solid; mp 130–133 °C (hexane–Et_2O).

IR (KBr): 1628, 1560, 1315 cm^{-1}.

^{1}H NMR (500 MHz): δ = 3.22 (3 H, s), 6.66 (1 H, dd, *J* = 8.2, 0.9 Hz), 6.77 (1 H, s), 6.92 (1 H, ddd, *J* = 7.8, 7.3, 0.9 Hz), 7.02 (1 H, dd, 7.8, 1.4 Hz), 7.10 (1 H, ddd, *J* = 8.2, 7.3, 1.4 Hz), 7.52 (2 H, d, *J* = 9.2 Hz), 8.15 (2 H, d, *J* = 9.2 Hz).

MS: *m*/*z* (%) = 284 (100, [M$^+$]).

Anal. Calcd for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85; S, 11.28. Found: C, 63.30; H, 4.51; N, 9.69; S, 11.19.

2-[(2-Nitrophenyl)methylthio]benzenamine

This compound was prepared from 2-aminobenzenethiol and 1-bromomethyl-2-nitrobenzene according to the procedure previously reported for the preparation of 2-(aminophenylthio)acetonitrile;[3] yield: 80%; mp 74–75 °C (hexane–Et_2O).

IR (KBr): 3466, 3368, 1607, 1519, 1344 cm^{-1}.

^1H NMR (500 MHz): δ = 4.24 (2 H, s), 4.32 (2 H, br s), 6.55 (1 H, dd, *J* = 7.8, 7.3, 1.4 Hz), 6.98 (1 H, dd, *J* = 7.8, 1.4), 6.98–7.01 (1 H, m), 7.05 (1 H, dd, *J* = 7.8, 1.4 Hz), 7.11 (1 H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.33–7.40 (2 H, m), 7.96–7.99 (1 H, m).

Anal. Calcd for $C_{13}H_{12}N_2O_2S$: C, 59.98; H, 4.65; N, 10.76; S, 12.32. Found: C, 59.96; H, 4.68; N, 10.74; S, 12.24.

***N*-{2-[(2-Nitrophenyl)methylthio]phenyl}formamide**

This compound was prepared from 2-[(2-nitrophenyl)methylthio]benzenamine as described for the preparation of [2-(formylamino)phenylthio]acetonitrile; yield: 76%; white solid; mp 102–105 °C (hexane–Et_2O–CH_2Cl_2).

IR (KBr): 3337, 1701, 1607, 1510, 1342 cm^{-1}.

^1H NMR (500 MHz): δ = 4.24 and 4.27 (combined 2 H, 2 s), 6.88–7.21 (2 H, m), 7.31–7.46 (4 H, m), 7.99–8.67 (4 H, m).

Anal. Calcd for $C_{14}H_{12}N_2O_3S$: C, 58.32; H, 4.20; N, 9.72; S, 11.12. Found: C, 58.45; H, 4.45; N, 9.68; S, 10.95.

1-Isocyano-2-[(2-nitrophenyl)methylthio]benzene (7)

This compound was prepared from *N*-{2-[(2-nitrophenyl)methylthio]phenyl}formamide as described for the preparation of **1a**, yield: 74%; yellow solid; mp 88–90 °C (hexane–Et_2O).

IR (KBr): 2120, 1609, 1522, 1350 cm^{-1}.

^1H NMR (500 MHz): δ = 4.53 (2 H, m), 7.24–7.31 (2 H, m), 7.30–7.43 (3 H, m), 7.42 (1 H, *J* = 7.8, 1.4 Hz), 7.48 (1 H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 8.01 (1 H, dd, *J* = 7.8, 1.4 Hz).

Anal. Calcd for $C_{14}H_{10}N_2O_2S$: C, 62.21; H, 3.73; N, 10.36; S, 11.86. Found: C, 62.19; H, 3.96; N, 10.34; S, 11.79.

2-(2-Nitrophenyl)-4*H*-1,4-benzothiazine (8)

To a stirred solution of *t*-BuOK (83 mg, 0.74 mmol) in THF (2 mL) at 0 °C was added a solution of **7** (0.20 g, 0.74 mmol) in THF (2 mL) dropwise. After 30 min stirring, the mixture was worked up in a manner similar to that described for the preparation of **2a**. Purification of the crude product by preparative TLC on silica gel gave **8** (76 mg, 38%); red solid; mp 92–94 °C (hexane–Et_2O).

IR (KBr): 3383, 1651, 1526, 1360 cm^{-1}.

^1H NMR (500 MHz): δ = 5.50 (1 H, br d, *J* = 5.5 Hz), 6.30 (1 H, d, *J* = 6.4 Hz), 6.46 (1 H, dd, *J* = 7.8, 1.4 Hz), 6.86 (1 H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 6.92 (1 H, dd, *J* = 7.8, 1.4 Hz), 6.98 (1 H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.34–7.40 (1 H, m), 7.48–7.52 (2 H, m), 7.76 (1 H, d, *J* = 8.2 Hz).

MS: *m*/*z* (%) = 270 (100, $[M^+]$).

Anal. Calcd for $C_{14}H_{10}N_2O_2S$: C, 62.21; H, 3.73; N, 10.36; S, 11.86. Found: C, 62.09; H, 3.85; N, 10.45; S, 11.79.

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