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SYNTHESIS OF 2-ALK(OR ARYL)OXY- AND 2-(ALKYL(OR ARYL)SULFANYL)-4*H*-3,1-BENZOTHIAZINE DERIVATIVES CARRYING A (*Z*)-HALOMETHYLIDENE SUBSTITUENT AT THE 4-POSITION

Kazuhiro Kobayashi* and Takashi Nogi

Division of Applied Chemistry, Department of Chemistry and Biotechnology, Graduate School of Engineering, Tottori University, 4-101 Koyama-minami, Tottori 680-8552, Japan; E-mail: kkoba@chem.tottori-u.ac.jp

Abstract – 2-Alk(or aryl)oxy-4-(*Z*)-(halomethylidene)-4*H*-3,1-benzothiazines were synthesized by the reaction of 2-(2,2-dihaloethenyl)phenyl isothiocyanates with sodium alk(or aryl)oxides. Similar treatment of the 2-(2,2-dibromoethenyl)phenyl isothiocyanates with sodium thiolates gave the corresponding 2-(alkyl(or aryl)sulfanyl)-4-(*Z*)-(bromomethylidene)-4*H*-3,1-benzothiazines. The above 2-aryloxybenzothiazine derivative underwent clean conversion to 2-aryloxy-4-(*Z*)-[(arylsulfanyl)methylidene]-4*H*-3,1-benzothiazines on treatment with sodium arenethiolates. 2-(Arylsulfanyl)-4-(*Z*)-[(arylsulfanyl)methylidene]-4*H*-3,1-benzothiazines were also synthesized by the reaction of 2-(2,2-dibromoethenyl)phenyl isothiocyanates with two equivalents of sodium arenethiolates.

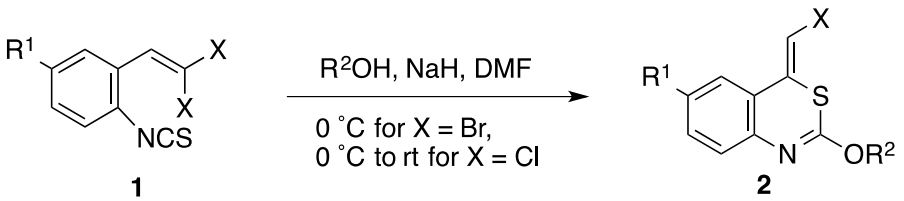
INTRODUCTION

The compounds based on the 4*H*-3,1-benzothiazine skeleton have recently aroused widespread interest among synthetic chemists, because some members of this family have been shown to possess a variety of biological activities.[1] Therefore, a number of interesting methods have been reported to prepare this class of compounds.[2] Several routes to 2-alk(or aryl)oxy-[3,4] or 2-(alkyl(or aryl)sulfanyl)-4*H*-3,1-benzothiazines[3-7] have also been reported. However, we became aware that to date no syntheses of their 4-halomethylidene derivatives have been achieved,[8] though Ding *et al*. have prepared 4-(*Z*)-(arylmethylidene)-2-(arylsulfanyl)-4*H*-3,1-benzothiazines by the reaction 2-(2-arylethynyl)benzenamines with carbon disulfide followed by copper-catalyzed S-arylation with aryl

bromides,[6] and a synthesis of 2-alkoxy-4-(1-iodopentylidene)-4*H*-3,1-benzothiazines based the reaction of 2-(hex-1-ynyl)phenyl isothiocyanate with sodium alkoxides followed by iodocyclization has been reported by Sashida *et al*.[5] On the other hand, we previously reported that 2-(2,2-dihaloethenyl)phenyl isothiocyanates (**1**) reacted with secondary amines and the resulting thiourea derivatives were treated with sodium hydride to afford *N*,*N*-dialkyl-4-(*Z*)-(halomethylidene)-4*H*-3,1-benzothiazin-2-amines.[9a] These prompted us to explore the possibility of the formation of 2-alk(or aryl)oxy-4-(*Z*)-(halomethylidene)-4*H*-3,1-benzothiazines (**2**) or 2-(alkyl(or aryl)sulfanyl)-4-(*Z*)-(halomethylidene)-4*H*-3,1-benzothiazines (**3**) by the reaction of these isothiocyanates (**1**) with sodium alk(or aryl)oxides or sodium thiolates. We now wish to report the achievement of these transformations and the synthesis of 2-aryloxy-4-(*Z*)-[(arylsulfanyl)methylidene]-4*H*-3,1-benzothiazine (**5**) and 2-(arylsulfanyl)-4-(*Z*)-[(arylsulfanyl)methylidene]-4*H*-3,1-benzothiazine derivatives (**6**).

RESULTS AND DISCUSSION

As shown in Scheme 1, we began our study by investigating reactions of 2-(2,2-dihaloethenyl)phenyl isothiocyanates (**1**) with alkoxides, generated from alcohols and sodium hydride, in DMF, in expectation of the formation of 2-alk(or aryl)oxy-4-(*Z*)-(halomethylidene)-4*H*-3,1-benzothiazines (**2**) through addition of alk(or aryl)oxides to the carbon atom of the isothiocyanate moiety followed by the intramolecular cyclization of the resulting thiocarbamate anion intermediates and elimination of a halide anion, as proposed in the previous paper.[9a] As expected, the reactions gave the desired products under the conditions summarized in Table 1, in which the yields of the products are also compiled. These data indicate that while the reactions using dibromoethenyl derivatives **1a**, **1c**, and **1d** proceeded smoothly at 0 ˚C to give the products generally in good yields, those using dichloroethenyl derivatives **1b** required an elevated temperature and an extended reaction time and the yields of the products considerably decreased. The alkoxide of an aliphatic alcohol, such as benzyl alcohol, was less reactive compared to aryloxides. As can be seen from Entry 2, the reaction of **1a** with sodium benzyloxide required a prolonged reaction time and the yield of the product **2b** was moderate-to fair. These reactions were highly *Z* selective affording each of these products as the sole isomer. The assignments of the stereochemistry of the products prepared in this study are based on NOE experiments as described in the previous report.[9a]



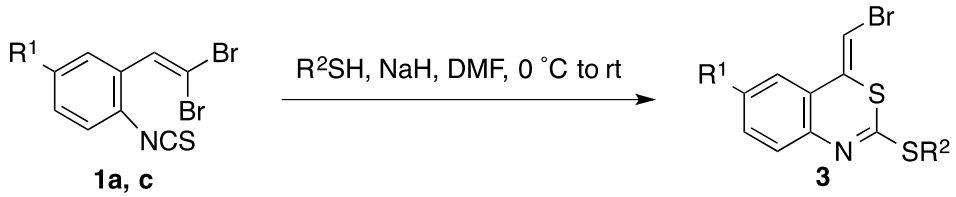
Scheme 1

Subsequently, we examined the reactions of **1** with sodium thiolates, generated *in situ* from thiols and sodium hydride (Scheme 2). It was found that using 2-(2,2-dibromoethenyl)phenyl isothiocyanate (**1a**) and 4-chloro-2-(2,2-dibromoethenyl)phenyl isothiocyanate (**1c**), a similar sequence proceeded smoothly at room temperature to afford the corresponding 2-(alkyl(or aryl)sulfanyl)-4-(*Z*)-(bromomethylidene)-4*H*-3,1-benzothiazines **3** in generally good yields as the sole stereoisomer (Table 2).

Table 1. Preparation of 2-alk(or aryl)oxy-4-(*Z*)-(halomethylidene)-4*H*-3,1-benzothiazines (**2**)

Entry	**1**	R^2	Temp	Time	**2**	Yield/%[a]
1	**1a** (R^1 = H, X = Br)	*p*-Tol	0 ˚C	0.5 h	**2a**	90
2	**1a**	Bn	0 ˚C	1 h	**2b**	64
3	**1a**	4-ClC_6H_4	0 ˚C	0.5 h	**2c**	93
4	**1a**	4-$MeOC_6H_4$	0 ˚C	0.5 h	**2d**	77
5	**1b** (R^1 = H, X = Cl)	*p*-Tol	rt	overnight	**2e**	40
6	**1b**	4-ClC_6H_4	rt	overnight	**2f**	23
7	**1b**	4-$MeOC_6H_4$	rt	overnight	**2g**	31
8	**1c** (R^1 = Cl, X = Br)	*p*-Tol	0 ˚C	0.5 h	**2h**	66
9	**1c**	naphthalen-2-yl	0 ˚C	0.5 h	**2i**	96
10	**1d** (R^1 = OMe, X = Br)	*p*-Tol	0 ˚C	1 h	**2j**	87
11	**1d**	quinolin-8-yl	0 ˚C	1 h	**2k**	70
12	**1d**	Bn	0 ˚C	2 h	**2l**	64

[a] Yields of isolated products.



Scheme 2

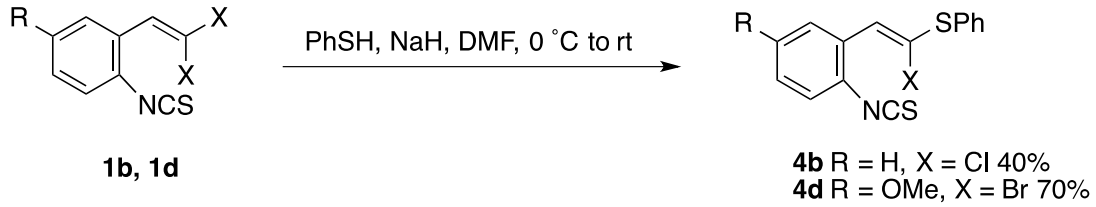
Table 2. Preparation of 2-(alkyl(or aryl)sulfanyl-4-(*Z*)-(halomethylidene)-4*H*-3,1-benzothiazines (**3**)

Entry	**1**	R^2	Time	**3**	Yield/%[a]
1	**1a** (R^1 = H, X = Br)	Ph	1 h	**3a**	75
2	**1a**	4-ClC_6H_4	1 h	**3b**	78
3	**1a**	4-$MeOC_6H_4$	1 h	**3c**	84
4	**1a**	naphthalen-2-yl	1 h	**3d**	90
5	**1a**	Bn	overnight	**3e**	42
6	**1c** (R^1 = Cl, X = Br)	Ph	1 h	**3f**	78
7	**1c**	4-ClC_6H_4	1 h	**3g**	52

[a] Yields of isolated products.

It should be mentioned that the reaction of 2-(2,2-dichloroethenyl)phenyl isothiocyanate (**1b**) or 2-(2,2-dibromoethenyl)-4-methoxyphenyl isothiocyanate (**1d**) with sodium benzenethiolate under the same conditions gave the corresponding 2-(*Z*)-[2-halo-2-(phenylsulfanyl)ethenyl]phenyl isothiocyanates (**4**) and the desired benzothiazine derivatives did not obtained at all, as shown in Scheme 3. It may be

assumed that the α-position of the dihaloethenyl moiety of **1b** is much more electrophilic toward benzenethiolate than that of **1a** due to the difference of the electron withdrawing properties between chlorine and bromine. For **1d**, the electron donating methoxy substituent may lower the electrophilicity of the isothiocyanate carbon toward benzenethiolate.

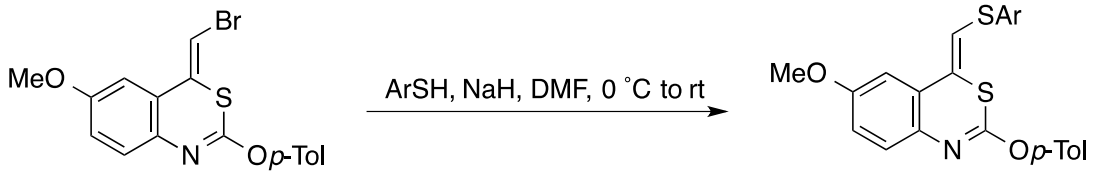


1b, 1d

4b R = H, X = Cl 40%
4d R = OMe, X = Br 70%

Scheme 3

We next turn attention to substitution of the bromo group of **2** for an arylsulfanyl group. In fact, treatment of **2j** with sodium thiolates in DMF at room temperature led smoothly to the formation of the corresponding 4-(*Z*)-[(arylsulfanyl)methylidene]-6-methoxy-2-(4-methylpheoxy)-4*H*-3,1-benzothiazines (**5**) in good yields, as depicted in Scheme 4. However, all attempts at similar replacement with an alkoxy group were unsuccessful. The reactions gave considerably intractable mixtures of products.

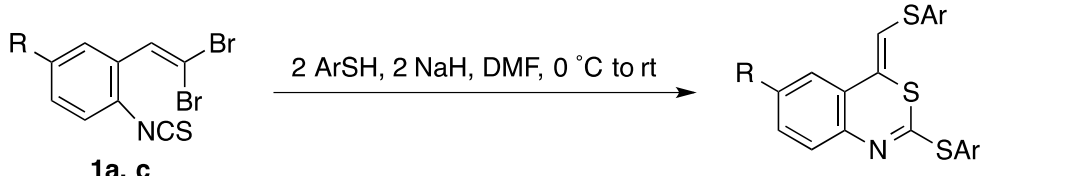


2j

5a R = Ph 74%
5b R = 4-ClC$_6$H$_4$ 86%
5c R = 4-MeOC$_6$H$_4$ 76%

Scheme 4

We then tried to convert 2-(2,2-dibromoethenyl)phenyl isothiocyanates (**1a**) and (**1c**) into 2-arylsulfanyl-4-(*Z*)-[(arylsulfanyl)methylidene]-4*H*-3,1-benzothiazines (**6**) in one-pot. The conversion was accomplished by exposure of the starting materials to two equivalents of sodium arenethiolates in DMF at 0 ˚C to room temperature, as shown in Scheme 5. The yields were moderate to fair.



1a, c

6a R = H, Ar = Ph 76%
6b R = H, Ar = 4-MeOC$_6$H$_4$ 61%
6c R = Cl, Ar = Ph 49%

Scheme 5

In conclusion, we have developed a convenient procedure for the preparation of novel 4-(*Z*)-(halomethylidene)-4*H*-3,1-benzothiazine derivatives. The procedure is useful because of its efficiency, the ready availability of the starting materials and the ease of operations, and its applicability to the synthesis of 4-(*Z*)-[(arylsulfanyl)methylidene]-4*H*-3,1-benzothiazine derivatives.

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 spectrometer (EI, TOF; 70eV). 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-(2,2-Halomethylidene)-1-isothiocyanatobenzenes (**1**) were prepared according to the reported method.[9] All other chemicals used in this study were commercially available.

General Procedure for the Preparation of 2-Alk(or aryl)oxybenzothiazines (2) and 2-(Alkyl(or aryl)sulfanyl)benzothiazines (3). To a stirred suspension of NaH (60% in mineral oil; 40 mg, 1.0 mmol) in DMF (3 mL) at 0 ˚C was added a solution of an alcohol or a thiol (1.0 mmol) in DMF (1 mL). After evolution of H_2 gas had ceased, a solution of **1** (1.0 mmol) in DMF (1 mL) was added. Stirring was then continued at the temperature and for the period indicated in Schemes 1 or 2 and Tables 1 or 2, respectively. Saturated aqueous NH_4Cl (20 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 (15 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on silica gel ($CHCl_3$/hexane 3: 1) to give the desired product.

4-(*Z*)-(Bromomethylidene)-2-(4-methylphenoxy)-4*H*-3,1-benzothiazine (2a): a yellow solid; mp 87–89 ˚C (hexane/CH_2Cl_2); IR (KBr) 1635 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 6.83 (s, 1H), 7.11–7.15 (m, 3H), 7.17–7.20 (m, 3H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.91, 100.53, 119.09, 121.35, 123.09, 126.90, 128.25, 129.85, 130.37, 133.48, 135.34, 141.69, 150.19, 157.99. HR-MS. Calcd for $C_{16}H_{12}BrNOS$ (M): 344.9823. Found: *m/z* 344.9824. Anal. Calcd for $C_{16}H_{12}BrNOS$: C, 55.50; H, 3.49; N, 4.05. Found: C, 55.47; H, 3.47; N, 3.92.

4-(*Z*)-(Bromomethylidene)-2-(phenylmethoxy)-4*H*-3,1-benzothiazine (2b): a yellow solid; mp 69–70 ˚C (hexane); IR (KBr) 1627 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.48 (s, 2H), 6.79 (s, 1H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.22–7.42 (m, 6H), 7.45 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 69.93, 100.04, 119.11, 123.18, 126.39,

127.81, 128.36, 128.52, 128.68, 130.39, 133.71, 135.66, 142.07, 157.99. HR-MS. Calcd for $C_{16}H_{12}BrNOS$ (M): 344.9823. Found: *m/z* 344.9832. Anal. Calcd for $C_{16}H_{12}BrNOS$: C, 55.50; H, 3.49; N, 4.05. Found: C, 55.51; H, 3.58; N, 4.01.

4-(*Z*)-(Bromomethylidene)-2-(4-chlorophenoxy)-4*H*-3,1-benzothiazine (2c): a beige solid; mp 160–161 ˚C (hexane/CH_2Cl_2); IR (KBr) 1636 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.86 (s, 1H), 7.12 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.18–7.23 (m, 3H), 7.33 (ddd, *J* = 8.0, 7.4, 1.1 Hz, 1H), 7.37 (d, *J* = 8.6 Hz, 2H), 7.47 (dd, *J* = 8.0, 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 100.84, 119.13, 123.07, 123.16, 127.21, 128.21, 129.37, 130.48, 130.97, 133.14, 141.32, 150.88, 157.61. HR-MS. Calcd for $C_{15}H_9BrClNOS$ (M): 364.9277. Found: *m/z* 364.9271. Anal. Calcd for $C_{15}H_9BrClNOS$: C, 49.14; H, 2.47; N, 3.82. Found: C, 48.98; H, 2.49; N, 3.86.

4-(*Z*)-(Bromomethylidene)-2-(4-methoxyphenoxy)-4*H*-3,1-benzothiazine (2d): an orange solid; mp 124–126 ˚C (hexane/CH_2Cl_2); IR (KBr) 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.83 (s, 3H), 6.83 (s, 1H), 6.91 (d, *J* = 9.2 Hz, 2H), 7.13–7.20 (m, 4H), 7.31 (ddd, *J* = 8.0, 7.4, 1.1 Hz, 1H), 7.46 (dd, *J* = 8.0, 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 55.59, 100.53, 114.30, 119.09, 122.58, 123.10, 126.90, 128.24, 130.38, 133.48, 141.70, 145.87, 157.18, 158.24. HR-MS. Calcd for $C_{16}H_{12}BrNO_2S$ (M): 360.9772. Found: *m/z* 360.9763. Anal. Calcd for $C_{16}H_{12}BrNO_2S$: C, 53.05; H, 3.34; N, 3.87. Found: C, 52.77; H, 3.34; N, 3.85.

4-(*Z*)-(Chloromethylidene)-2-(4-methylphenoxy)-4*H*-3,1-benzothiazine (2e): a yellow solid; mp 72–74 ˚C (hexane); IR (KBr) 1634 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.37 (s, 3H), 6.67 (s, 1H), 7.12 (d, *J* = 8.6 Hz, 2H), 7.15 (ddd, *J* = 8.0, 7.4, 1.1 Hz, 1H), 7.18–7.21 (m, 3H), 7.30 (ddd, *J* = 8.0, 7.4, 1.1 Hz, 1H), 7.43 (dd, *J* = 8.0, 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.91, 111.15, 117.82, 121.37, 122.92, 126.87, 128.31, 129.85, 130.30, 130.75, 135.35, 141.56, 150.20, 157.71. HR-MS. Calcd for $C_{16}H_{12}ClNOS$ (M): 301.0328. Found: *m/z* 301.0339. Anal. Calcd for $C_{16}H_{12}ClNOS$: C, 63.68; H, 4.01; N, 4.64. Found: C, 63.63; H, 4.27; N, 6.37.

4-(*Z*)-(Chloromethylidene)-2-(4-chlorophenoxy)-4*H*-3,1-benzothiazine (2f): a pale-yellow solid; mp 147–149 ˚C (hexane/CH_2Cl_2); IR (KBr) 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.69 (s, 1H), 7.12 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.17–7.22 (m, 3H), 7.32 (ddd, *J* = 8.0, 7.4, 1.1 Hz, 1H), 7.36 (d, *J* = 8.6 Hz, 2H), 7.44 (dd, *J* = 8.0, 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 111.45, 117.85, 122.98, 123.09, 127.16, 128.27, 129.37, 130.41, 130.98 (2 overlapped Cs), 141.17, 150.87, 157.33. HR-MS. Calcd for $C_{15}H_9Cl_2NOS$ (M): 320.9782. Found: *m/z* 320.9795. Anal. Calcd for $C_{15}H_9Cl_2NOS$: C, 55.92; H, 2.82; N, 4.35. Found: C, 55.70; H, 2.79; N, 4.24.

4-(*Z*)-(Chloromethylidene)-2-(4-methoxyphenoxy)-4*H*-3,1-benzothiazine (2g): a yellow solid; mp 98–99 ˚C (hexane/CH_2Cl_2); IR (KBr) 1631 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.82 (s, 3H), 6.67 (s, 1H), 6.91 (d, *J* = 9.2 Hz, 2H), 7.13–7.20 (m, 4H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.43 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 55.59, 111.16, 114.29, 117.81, 122.59, 122.92, 126.85, 128.29, 130.31, 130.74, 141.56, 145.86, 157.19,

157.96. HR-MS. Calcd for $C_{16}H_{12}ClNO_2S$ (M): 317.0277. Found: *m/z* 317.0281. Anal. Calcd for $C_{16}H_{12}ClNO_2S$: C, 60.47; H, 3.81; N, 4.41. Found: C, 60.43; H, 3.81; N, 4.36.

4-(*Z*)-(Bromomethylidene)-6-chloro-2-(4-methylphenoxy)-4*H*-3,1-benzothiazine (2h): a yellow solid; mp 146–147 ˚C (hexane/CH_2Cl_2); IR (KBr) 1626 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.37 (s, 3H), 6.85 (s, 1H), 7.07 (d, *J* = 8.6 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.25 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.43 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.91, 101.79, 120.38, 121.33, 123.02, 129.48, 129.89, 130.29, 132.11, 132.42, 135.54, 140.35, 150.06, 158.51. HR-MS. Calcd for $C_{16}H_{11}BrClNOS$ (M): 378.9433. Found: *m/z* 378.9418. Anal. Calcd for $C_{16}H_{11}BrClNOS$: C, 50.48; H, 2.91; N, 3.68. Found: C, 50.56; H, 3.06; N, 3.59.

4-(*Z*)-(Bromomethylidene)-6-chloro-2-(naphthalen-2-yloxy)-4*H*-3,1-benzothiazine (2i): a pale-yellow solid; mp 173–174 ˚C (hexane/CH_2Cl_2); IR (KBr) 1622 cm^{-1}; ^1H NMR (THF-d_8) δ 6.96 (d, *J* = 8.6 Hz, 1H), 7.25 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.35 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.36 (s, 1H), 7.40–7.46 (m, 2H), 7.68 (d, *J* = 1.7 Hz, 1H), 7.70 (d, *J* = 2.3 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (THF-d_8) δ 103.11, 118.46, 120.53, 121.37, 123.42, 125.69, 126.46, 127.61, 127.66, 129.12, 129.54, 130.24, 131.69, 131.72, 132.15, 134.04, 140.37, 150.34, 158.30. HR-MS. Calcd for $C_{19}H_{11}BrClNOS$ (M): 414.9433. Found: *m/z* 414.9419. Anal. Calcd for $C_{19}H_{11}BrClNOS$: C, 54.76; H, 2.66; N, 3.36. Found: C, 54.55; H, 2.78; N, 3.21.

4-(*Z*)-(Bromomethylidene)-6-methoxy-2-(4-methylphenoxy)-4*H*-3,1-benzothiazine (2j): a pale-yellow solid; mp 104–105 ˚C (hexane/CH_2Cl_2); IR (KBr) 1636, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.37 (s, 3H), 3.81 (s, 3H), 6.83 (s, 1H), 6.89 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.95 (d, *J* = 2.9 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 20.91, 55.59, 100.31, 107.60, 116.35, 119.67, 121.29, 129.50, 129.83, 133.69, 135.18, 135.28, 150,32, 155.95, 158.26. HR-MS. Calcd for $C_{17}H_{14}BrNO_2S$ (M): 374.9929. Found: *m/z* 374.9946. Anal. Calcd for $C_{17}H_{14}BrNO_2S$: C, 54.27; H, 3.75; N, 3.72; S, 8.52. Found: C, 54.15; H, 3.80; N, 3.64; S, 8.51.

4-(*Z*)-(Bromomethylidene)-6-methoxy-2-(quinolin-8-oxy)-4*H*-3,1-benzothiazine (2k): a pale-yellow solid; mp 167–168 ˚C (hexane/CH_2Cl_2); IR (KBr) 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.78 (s, 3H), 6.79 (dd, *J* = 9.2, 2.9 Hz, 1H), 6.84 (s, 1H), 6.87 (d, *J* = 8.6 Hz, 1H), 6.95 (d, *J* =2.9 Hz, 1H), 7.42 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.56 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.61 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.74 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.19 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.91 (dd, *J* = 4.0, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 55.54, 100.19, 107.48, 116.23, 119.80, 121.67, 121.70, 125.66, 126.12, 129.38, 129.52, 133.85, 135.37, 135.90, 141.34, 148.93, 150.55, 156.83, 158.15. HR-MS. Calcd for $C_{19}H_{13}BrN_2O_2S$ (M): 411.9881. Found: *m/z* 411.9897. Anal. Calcd for $C_{19}H_{13}BrN_2O_2S$: C, 55.22; H, 3.17; N, 6.78; S, 7.76. Found: C, 55.06; H, 3.24; N, 6.53; S, 7.90.

4-(*Z*)-(Bromomethylidene)-6-methoxy-2-(phenylmethoxy)-4*H*-3,1-benzothiazine (2l): a yellow solid; mp 110–112 ˚C (hexane/CH_2Cl_2); IR (KBr) 1636 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.82 (s, 3H), 5.45 (s, 2H),

6.78 (s, 1H), 6.94–6.96 (m, 2H), 7.24 (d, *J* = 9.2 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.44 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 55.61, 69.72, 99.83, 107.61, 116.53, 119.63, 128.29, 128.45, 128.50, 128.97, 133.93, 135.74, 135.82, 156.11, 157.88. HR-MS. Calcd for $C_{17}H_{14}BrNO_2S$ (M): 374.9929. Found: *m/z* 374.9941. Anal. Calcd for $C_{17}H_{14}BrNO_2S$: C, 54.27; H, 3.75; N, 3.72; S, 8.52. Found: C, 53.95; H, 3.77; N, 3.54; S, 8.92.

4-(*Z*)-(Bromomethylidene)-2-(phenylsulfanyl)-4*H*-3,1-benzothiazine (3a): a yellow solid; mp 88–90 ˚C (hexane/CH_2Cl_2); IR (KBr) 1603, 1542 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.71 (s, 1H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.26 (d, *J* = 7.4 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.43–7.49 (m, 3H), 7.67 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 100.89, 119.35, 123.21, 127.46, 127.94, 128.60, 129.25, 130.13, 130.41, 132.73, 135.83, 142.04, 159.62. HR-MS. Calcd for $C_{15}H_{10}BrNS_2$ (M): 346.9438. Found: *m/z* 346.9451. Anal. Calcd for $C_{15}H_{10}BrNS_2$: C, 51.73; H, 2.89; N, 4.02; S, 18.41. Found: C, 51.58; H, 3.09; N, 3.86; S, 18.75.

4-(*Z*)-(Bromomethylidene)-2-[(4-chlorophenyl)sulfanyl]-4*H*-3,1-benzothiazine (3b): a yellow solid; mp 123–124 ˚C (hexane/CH_2Cl_2); IR (KBr) 1605, 1546 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.74 (s, 1H), 7.23–7.26 (m, 2H), 7.36–7.39 (m, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.59 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 101.79, 119.46, 123.30, 126.02, 128.12, 128.59, 129.48, 130.47, 132.46, 136.54, 136.90, 141.88, 158.65. HR-MS. Calcd for $C_{15}H_9BrClNS_2$ (M): 380.9048. Found: *m/z* 380.9060. Anal. Calcd for $C_{15}H_9BrClNS_2$: C, 47.08; H, 2.37; N, 3.66. Found: C, 47.27; H, 2.56; N, 3.49.

4-(*Z*)-(Bromomethylidene)-2-[(4-methoxyphenyl)sulfanyl]-4*H*-3,1-benzothiazine (3c): a yellow solid; mp 132–135 ˚C (hexane/CH_2Cl_2); IR (KBr) 1588, 1542 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 3H), 6.69 (s, 1H), 6.97 (d, *J* = 8.6 Hz, 2H), 7.21 (td, *J* = 7.4, 1.7 Hz, 1H), 7.28 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.35 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.59 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 55.42, 100.61, 114.87, 117.38, 119.07, 123.13, 127.78, 128.56, 130.41, 132.90, 138.05, 142.12, 161.38, 161.46. HR-MS. Calcd for $C_{16}H_{12}BrNOS_2$ (M): 376.9544. Found: *m/z* 376.9544. Anal. Calcd for $C_{16}H_{12}BrNOS_2$: C, 50.80; H, 3.20; N, 3.70. Found: C, 50.94; H, 3.20; N, 3.64.

4-(*Z*)-(Bromomethylidene)-2-[(naphthalen-2-yl)sulfanyl]-4*H*-3,1-benzothiazine (3d): a yellow solid; mp 114–115 ˚C (hexane/CH_2Cl_2); IR (KBr) 1603, 1542 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.71 (s, 1H), 7.20–7.25 (m, 2H), 7.33–7.37 (m, 2H), 7.53–7.59 (m, 2H), 7.68 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.86–7.89 (m, 3H), 8.19 (d, *J* = 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 101.46, 119.46, 123.25, 124.91, 126.74, 127.50, 127.82, 127.98, 128.14, 128.61, 128.80, 130.41, 131.76, 132.71, 133.49, 133.59, 135.61, 142.05, 159.50. HR-MS. Calcd for $C_{19}H_{12}BrNS_2$ (M): 396.9595. Found: *m/z* 396.9614. Anal. Calcd for $C_{19}H_{12}BrNS_2$: C, 57.29; H, 3.04; N, 3.52. Found: C, 57.23; H, 3.08; N, 3.33.

4-(*Z*)-(Bromomethylidene)-2-[(phenylmethyl)sulfanyl]-4*H*-3,1-benzothiazine (3e): a yellow solid; mp 72–74 ˚C (hexane/CH_2Cl_2); IR (KBr) 1601, 1548 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.50 (s, 2H), 6.75 (s, 1H),

7.24–7.41 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 35.32, 101.15, 120.05, 123.55, 127.46, 127.57, 128.11, 128.58, 129.18, 130.42, 132.39, 136.87, 141.82, 157.70. HR-MS. Calcd for $C_{16}H_{12}BrNS_2$ (M): 360.9595. Found: *m/z* 360.9613. Anal. Calcd for $C_{16}H_{12}BrNS_2$: C, 53.04; H, 3.34; N, 3.87. Found: C, 52.90; H, 3.44; N, 3.89.

4-(*Z*)-(Bromomethylidene)-6-chloro-2-(phenylsulfanyl)-4*H*-3,1-benzothiazine (3f): a yellow solid; mp 120–121 ˚C (hexane/CH_2Cl_2); IR (KBr) 1598, 1547 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.74 (s, 1H), 7.19 (d, *J* = 8.6 Hz, 1H), 7.31 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.36 (d, *J* = 2.3 Hz, 1H), 7.43–7.51 (m, 3H), 7.67 (dd, *J* = 8.0, 1.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 102.18, 120.61, 123.16, 127.08, 129.33, 129.86, 130.33, 130.36, 131.67, 133.15, 135.94, 140.64, 160.50. HR-MS. Calcd for $C_{15}H_9BrClNS_2$ (M): 380.9048. Found: *m/z* 380.9040. Anal. Calcd for $C_{15}H_9BrClNS_2$: C, 47.08; H, 2.37; N, 3.66; 16.75. Found: C, 47.42; H, 2.63; N, 3.58; S, 16.83.

4-(*Z*)-(Bromomethylidene)-6-chloro-2-[(4-chlorophenyl)sulfanyl]-4*H*-3,1-benzothiazine (3g): an orange solid; mp 156–158 ˚C (decomp) (hexane/$CHCl_3$); IR (KBr) 1599, 1550 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.76 (s, 1H), 7.17 (d, *J* = 8.6 Hz, 1H), 7.31 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.36 (d, *J* = 2.3 Hz, 1H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.58 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 102.56, 120.72, 123.23, 125.66, 129.54, 129.84, 130.41, 131.41, 133.36, 136.75, 136.98, 140.47, 159.46. HR-MS. Calcd for $C_{15}H_8BrCl_2NS_2$ (M): 414.8659. Found: *m/z* 414.8665. Anal. Calcd for $C_{15}H_8BrCl_2NS_2$: C, 43.19; H, 1.93; N, 3.36. Found: C, 43.07; H, 1.99; N, 3.32.

1-(*Z*)-[Halo(phenylsulfanyl)methylidene]-2-isothiocyanatobenzenes (4). These compounds were obtained by treating **1b** or **1d** with NaSPh as described in General Procedure (0 ˚C to rt; 4 h).

1-(*Z*)-[Chloro(phenylsulfanyl)methylidene]-2-isothiocyanatobenzene (4b): yield: 60%; a pale-pink oil; R_f 0.40 (hexane); IR (neat) 2057 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.25–7.38 (m, 7H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.66 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 126.82, 126.90, 128.10, 129.19 (2 overlapped Cs), 129.37, 129.97, 130.16, 131.13, 131.21, 131.24, 131.82, 132.69. HR-MS. Calcd for $C_{15}H_{10}ClNS_2$ (M): 302.9943. Found: *m/z* 302.9933. Anal. Calcd for $C_{15}H_{10}ClNS_2$: C, 59.30; H, 3.32; N, 4.61. Found: C, 59.13; H, 3.39; N, 4.43.

1-(*Z*)-[Bromo(phenylsulfanyl)methylidene]-2-isothiocyanato-5-methoxybenzene (4d): yield: 70%; a pale-yellow oil; R_f 0.28 ($CHCl_3$/hexane); IR (neat) 2077, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 3H), 6.84 (dd, *J* = 9.2, 2.9 Hz, 1H), 7.19 (d, *J* = 9.2 Hz, 1H), 7.22 (d, *J* = 2.9 Hz, 1H), 7.33–7.41 (m, 5H), 7.50 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.61, 114.53, 115.34, 120.68, 122.49, 127.92, 128.14, 129.22, 131.04 (2 overlapped Cs), 132.94, 133.06, 135.52, 157.94. HR-MS. Calcd for $C_{16}H_{12}BrNOS_2$ (M): 376.9544. Found: *m/z* 376.9537. Anal. Calcd for $C_{16}H_{12}BrNOS_2$: C, 50.80; H, 3.20; N, 3.70. Found: C, 50.71; H, 3.22; N, 3.60.

Typical Procedure for the Preparation of 2-Aryloxy-4-(*Z*)-[(arylsulfanyl)methylidene]-4*H*-3,1-benzothiazines (5). 6-Methoxy-2-(4-methylphenoxy)-4-(*Z*)-[(phenylsulfanyl)methylidene]-4*H*-3,1-benzothiazine (5a). To a stirred suspension of NaH (60% in mineral oil; 19 mg, 0.47 mmol) in DMF (2 mL) at 0 ˚C was added PhSH (52 mg, 0.47 mmol) dropwise. After evolution of H_2 gas had ceased, a solution of **2j** (0.18 g, 0.47 mmol) in DMF (2 mL) was added dropwise and the temperature was raised to rt. Stirring was continued for 2 h at the same temperature and the mixture was worked up and purified as described in the above General Procedure to give **5a** (0.14 g, 74%); a yellow solid; mp 126–127 ˚C (hexane/CH_2Cl_2); IR (KBr) 1637, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.37 (s, 3H), 3.81 (s, 3H), 6.81 (s, 1H), 6.86 (dd, *J* = 9.2, 2.9 Hz, 1H), 6.99 (d, *J* = 2.9 Hz, 1H), 7.10 (d, *J* = 9.2 Hz, 1H), 7.13 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 2H), 7.27 (t, *J* = 7.4 Hz, 1H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.40 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 20.91, 55.78, 107.99, 108.00, 115.64, 117.32, 117.33, 120.76, 121.33, 127.17, 129.25, 129.41, 129.81, 134.86, 134.97, 135.09, 150.43, 156.11, 158.20. HR-MS. Calcd for $C_{23}H_{19}NO_2S_2$ (M): 405.0857. Found: *m/z* 405.0874. Anal. Calcd for $C_{23}H_{19}NO_2S_2$: C, 68.12; H, 4.72; N, 3.45; S, 15.81. Found: C, 68.37; H, 4.73; N, 3.40; S, 15.92.

4-(*Z*)-{[(4-Chlorophenyl)sulfanyl]methylidene}-6-methoxy-2-(4-methylphenoxy)-4*H*-3,1-benzothiazine (5b): a yellow solid; mp 125–127 ˚C (hexane/CH_2Cl_2); IR (KBr) 1631, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.37 (s, 3H), 3.81 (s, 3H), 6.74 (s, 1H), 6.88 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.99 (d, *J* = 2.9 Hz, 1H), 7.12 (d, *J* = 8.6 Hz, 3H), 7.18 (d, *J* = 8.6 Hz, 2H), 7.31 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 20.91, 55.60, 108.01, 115.88, 115.94, 120.48, 121.31, 129.34, 129.37, 129.82, 130.46, 131.16, 133.21, 133.53, 134.94, 135.14, 150.40, 155.99, 158.22. HR-MS. Calcd for $C_{23}H_{18}ClNO_2S_2$ (M): 439.0467. Found: *m/z* 439.0478. Anal. Calcd for $C_{23}H_{18}ClNO_2S_2$: C, 62.79; H, 4.12; N, 3.18. Found: C, 62.67; H, 4.14; N, 3.13.

6-Methoxy-4-(*Z*)-{[(4-methoxyphenyl)sulfanyl]methylidene}-2-(4-methylphenoxy)-4*H*-3,1-benzothiazine (5c): a yellow solid; mp 91–92 ˚C (hexane/CH_2Cl_2); IR (KBr) 1634 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.37 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 6.73 (s, 1H), 6.83 (dd, *J* = 9.2, 2.9 Hz, 1H), 6.89 (d, *J* = 9.2 Hz, 2H), 6.93 (d, *J* = 2.9 Hz, 1H), 7.07 (d, *J* = 9.2 Hz, 1H), 7.13 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 2H), 7.38 (d, *J* = 9.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 20.90, 55.41, 55.55, 107.89, 114.89, 115.34, 119.99, 120.90, 121.32, 125.26, 126.56, 129.13, 129.79, 132.42, 134.71, 135.05, 150.45, 156.03, 158.16, 159.54. HR-MS. Calcd for $C_{24}H_{21}NO_3S_2$ (M): 435.0963. Found: *m/z* 435.0968. Anal. Calcd for $C_{24}H_{21}NO_3S_2$: C, 66.18; H, 4.86; N, 3.22; S, 14.72. Found: C, 66.39; H, 4.84; N, 3.16; S, 14.78.

Typical Procedure for the Preparation of 2-(Arylsulfanyl)-4-(*Z*)-[(arylsulfanyl)methylidene]-4*H*-3,1-benzothiazines (6). 2-(Phenylsulfanyl)-4-(*Z*)-[(phenylsulfanyl)methylidene]-4*H*-3,1-benzothiazine (6a). To a stirred suspension of NaH (60% in mineral oil; 40 mg, 1.0 mmol) in DMF (5 mL) at 0 ˚C was added PhSH (0.11 g, 1.0 mmol) dropwise. After evolution of H_2 gas had ceased, a solution of **1a** (0.32 g, 1.0 mmol) in DMF (2 mL) was added dropwise and the temperature was raised to rt. Stirring was

continued for 2 h at the same temperature and the mixture was worked up and purified as described in the above General Procedure to give **6a** (0.29 g, 76%); a yellow solid; mp 98–99 ˚C (hexane/CH_2Cl_2); IR (KBr) 1600, 1542 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.71 (s, 1H), 7.20–7.26 (m, 3H), 7.30–7.35 (m, 5H), 7.39–7.48 (m, 4H), 7.67 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 118.46, 120.54, 123.53, 126.63, 127.14, 127.62, 127.72, 127.76, 128.30, 129.19, 129.44, 129.67, 129.96, 134.97, 135.71, 141.69, 159.78. HR-MS. Calcd for $C_{21}H_{15}NS_3$ (M): 377.0367. Found: *m/z* 377.0384. Anal. Calcd for $C_{21}H_{15}NS_3$: C, 66.81; H, 4.00; N, 3.71; S, 25.48. Found: C, 66.44; H, 3.95; N, 3.71; S, 25.37.

2-[(4-Methoxyphenyl)sulfanyl]-4-(*Z*)-{[(4-methoxyphenyl)sulfanyl]methylidene}-4*H*-3,1-benzothiazine (6b): yellow oil; R_f 0.28 (CH_2Cl_2/hexane 1:1); IR (neat) 1591, 1547 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.80 (s, 3H), 3.86 (s, 3H); 6.62 (s, 1H), 6.86 (d, *J* = 9.2 Hz, 2H), 6.96 (d, *J* = 8.6 Hz, 2H), 7.17 (td, *J* = 7.4, 1.1 Hz, 1H), 7.24 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.28–7.35 (m, 4H), 7.60 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 55.40 (2 overlapped Cs), 114.79, 114.83, 117.81, 120.40, 120.61, 123.35, 125.28, 125.38, 127.52, 128.19, 129.38, 132.37, 137.92, 141.64, 159.48, 161.30, 161.39. HR-MS. Calcd for $C_{23}H_{19}NO_2S_3$ (M): 437.0578. Found: *m/z* 437.0561. Anal. Calcd for $C_{23}H_{19}NO_2S_3$: C, 63.13; H, 4.38; N, 3.20. Found: C, 63.08; H, 4.44; N, 3.22.

6-Chloro-2-(phenylsulfanyl)-4-(*Z*)-[(phenylsulfanyl)methylidene]-4*H*-3,1-benzothiazine (6c): a yellow oil; R_f 0.36 (AcOEt/hexane 1:9); IR (KBr) 1594, 1540 cm^{-1}; ^1H NMR (500 MHz) δ 6.37 (s, 1H), 7.15 (d, *J* = 8.6 Hz, 1H), 7.23–7.29 (m, 2H), 7.30–7.36 (m, 5H), 7.41–7.48 (m, 3H), 7.66 (dd, *J* = 8.0, 1.7 Hz, 2H); ^{13}C NMR (125 MHz) δ 120.66, 121.90, 123.29, 125.11, 127.42, 127.47, 129.22, 129.28, 129.41, 129.51, 129.81, 130.11, 132.88, 134.48, 135.78, 140.19, 160.44. HR-MS. Calcd for $C_{21}H_{14}ClNS_3$ (M): 410.9977. Found: *m/z* 410.9972. Anal. Calcd for $C_{21}H_{14}ClNS_3$: C, 61.22; H, 3.43; N, 3.40. Found: C, 61.67; H, 3.44; N, 3.39.

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