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Two-pot synthesis of *N*,*N*-disubstituted 4*H*-3,1-benzothiazin-2-amines from aryl(2-isothiocyanatophenyl)methanones and secondary amines

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ABSTRACT

A convenient synthesis of *N*,*N*-disubstituted 4*H*-3,1-benzothiazin-2-amines from aryl(2-isothiocyanatophenyl)methanones using a two-pot procedure has been developed. Thus, treatment of these isothiocyanato ketones with secondary amines gave the corresponding keto thioureas, which were allowed to react with sodium borohydride or methylmagnesium bromide to afford 1,1-dialkyl-3-{2-[aryl(hydroxy)methyl]phenyl}thioureas or 1,1-dialkyl-3-[2-(1-aryl-1-hydroxyethyl)phenyl]thioureas, respectively, in one pot. Hydrobromic acid-mediated cyclization of these hydroxy thiourea precursors provided the desired 4*H*-3,1-benzothiazin-2-amines.

1. Introduction

Some compounds having the 4*H*-3,1-benzothiazin-2-amine structure have recently been reported to exhibit biological activities,[1] and several efficient routes to 4*H*-3,1-benzothiazin-2-amine derivatives have been published.[2] As a part of our studies on the synthesis of heterocyclic compounds utilizing *o*-functionalized phenyl isothiocyanates,[3] we recently described the synthesis of 2-(2-dialkylamino-4*H*-3,1-benzothiazin-2-yl)acetic acid derivatives by the reaction of 3-(2-isothiocyanatophenyl)prop-2-enoic acid derivatives with secondary amines.[3d] In this paper we wish to report that a new class of 4*H*-3,1-benzothiazin-2-amines, *N*,*N*-disubstituted 4-aryl-4*H*-3,1-benzothiazin-2-amines, can be prepared by easily operated hydrobromic acid-mediated cyclization of 1,1-dialkyl-3-[2-(1-aryl-1-hydroxyalkyl)phenyl]thioureas, readily available from aryl(2-isothiocyanatophenyl)methanones and secondary amines. After completion of this work, we were aware of a report on the synthesis of *N*,*N*-disubstituted 5-aryl-1,5-dihydro-2,4-benzothiazepine-3-amines hydrochlorides by cyclization of 1,1-dialkyl-3-{2-[hydroxy(phenyl)methyl]phenylmethyl}thioureas mediated by dry hydrogen chloride,[4] which is hazardous and tedious to handle.

2. Results and discussion

The synthesis of *N*,*N*-disubstituted 4-aryl-4*H*-3,1-benzothiazin-2-amines **4** from aryl(2-isothiocyanatophenyl)methanones **1** has been accomplished according to the sequence illustrated in Scheme 1. The precursors for **4**, 1,1-dialkyl-3-{2-[aryl(hydroxy)methyl]phenyl}thioureas **3a**–**c**, **3e**–**g**, and **3i**–**k**, or 1,1-dialkyl-3-[2-(1-aryl-1-hydroxyethyl)phenyl]thioureas **3d** and **3h**, were prepared in one pot by an easy two-step sequence. Thus, compounds **1** were first treated with secondary amines in EtOH (for **3a**–**c**, **3e**–**g**, and **3i**–**k**) or THF (for **3d** and **3h**) to generate the corresponding keto thiourea derivatives **2**, which were then allowed to react with sodium borohydride or methylmagnesium bromide, respectively, to afford, after aqueous workup followed by purification using column chromatography on silica gel, the desired hydroxy thiourea precursors **3** in good to excellent yields from **1** as summarized in Table 1. It should be noted that an attempt was made to convert **2a** into 1,1-diethyl-3-[2-[1-hydroxy-1-phenylpropyl]phenyl]thiourea (**3**; R^1=R^2=H, R^3=R^4=R^5=Et) on treatment with ethylmagnesium bromide, but it resulted in the formation of **3a**.

We envisaged that the desired products **4** could be accessible through an acid-mediated cyclization of **3**. First, 1,1-diethyl-3-{2-[hydroxy(phenyl)methyl]phenyl}thiourea (**3a**) was treated with an equimolar amount of concentrated hydriodic acid. However, a considerably complicated mixture of products was obtained, and only low yield (15%) of the desired product, *N*,*N*-diethyl-4-phenyl-4*H*-3,1-benzothiazin-2-amine (**4a**), could be isolated. Subsequently, treatment of the precursors **3** with an equimolar amount of

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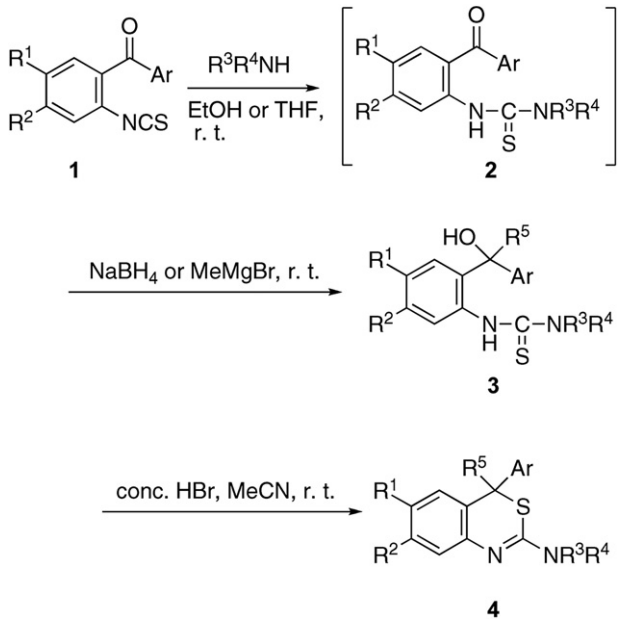


Scheme 1.

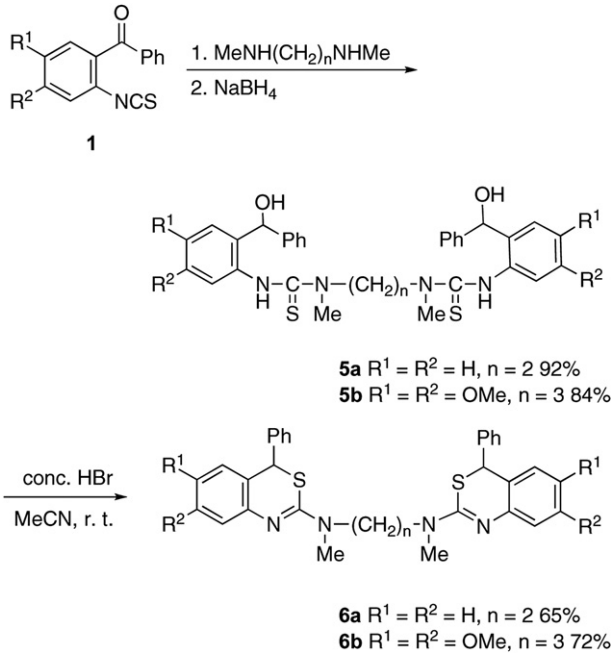
Table 1
Preparation of *N*,*N*-disubstituted 4*H*-3,1-benzothiazin-2-amines **4**

Entry	**1**[a]	R^2R^3NH	R^4	**3**	Yield[b] (%)	HBr (equiv)	Time	**4**	Yield[b] (%)
1	**1a**	Et_2NH	H	**3a**	88	1	2.5 h	**4a**	85
2	**1a**	Piperidine	H	**3b**	76	1	2 h	**4b**	69
3	**1a**	Morpholine	H	**3c**	93	1	2 h	**4c**	73
4	**1a**	Pyrrolidine	Me	**3d**	82	1	5 h	**4d**	59
5	**1b**	Et_2NH	H	**3e**	87	2	[c]	**4e**	78
6	**1b**	PhNHMe	H	**3f**	86	2	[c]	**4f**	70
7	**1c**	Et_2NH	H	**3g**	97	1	1.5 h	**4g**	70
8	**1c**	Piperidine	Me	**3h**	86	1	5 h	**4h**	53
9	**1d**	Et_2NH	H	**3i**	98	1	5 min	**4i**	80
10	**1d**	PhNHMe	H	**3j**	96	1	5 min	**4j**	66
11	**1e**	Et_2NH	H	**3k**	88	1	5 min	**4k**	76

[a] **1a** (R^1=R^2=H, Ar=Ph), **1b** (R^1=Cl, R^2=H, Ar=Ph), **1c** (R^1=R^2=H, Ar=4-ClC_6H_4), **1d** (R^1=R^2=H, Ar=4-$MeOC_6H_4$), **1e** (R^1=R^2=OMe, Ar=Ph).
[b] Yields of isolated products.
[c] Overnight.

concentrated hydrobromic acid at room temperature proved to afford the desired *N*,*N*-dialkyl-4*H*-3,1-benzothiazin-2-amines **4** in satisfactory yields. Similarly, the other 10 products **4b**–**k** were obtained. All products **4** have IR, ^1H and ^{13}C NMR, and mass spectra, which are consistent with the assigned structures and all gave satisfactory analytical data (see Experimental section). Table 1 also summarizes the yields of the products **4** along with reaction conditions for the formation of **4**. The hydrobromic mediated cyclization proceeded smoothly in general. Especially, the precursors derived from (2-isothiocyanatophenyl)(4-methoxyphenyl)methanone (1d) and (2-isothiocyanato-4,5-dimethoxyphenyl)phenylmethanone (**1e**) proved to be very reactive to provide the corresponding desired products **4i**–**k** (entries 9–11). However, the precursors from (5-chloro-2-isothiocyanatophenyl)phenylmethanone (**1b**) did proceed very sluggishly under the same conditions. Increasing the equivalents of concentrated hydrobromic acid from 1.0 to 2.0 and extending the reaction time overnight gave satisfactory yields of the desired products **4e** and **4f** (entries 5 and 6).

In order to demonstrate the usefulness of the present procedure, the synthesis of an *N*,*N*′-bis(4*H*-3,1-benzothiazin-4-yl)-1,2-ethanediamine derivative **6a** and an *N*,*N*′-bis(4*H*-3,1-benzothiazin-4-yl)-1,3-propanediamine derivative **6b** was carried out as illustrated in Scheme 2. Addition of *N*,*N*′-dimethyl-1,2-ethanediamine and *N*,*N*′-dimethyl-1,3-propanediamine to 2 M amounts of the appropriate aryl(2-isothiocyanatopheny)methanones **1a** and **1e**, respectively, followed by sodium borohydride reduction proceeded uneventfully, affording the corresponding bisthiourea precursors **5a** and **5b** in good yields. The cyclization of **5** mediated by an equivalent of concentrated hydrobromic acid completed within 1 h for **5a** and 5 min for **5b** at room temperature and the desired bis(benzothiazinyl)alkanediamines **6a** and **6b** could be obtained in fair yields as a mixture of diastereomers (ca. 1:1) in each case.



Scheme 2.

In summary, the results reported above demonstrate that addition of secondary amines to the isothiocyanato carbon of aryl(2-isothiocyanatophenyl)methanones, followed by treatment with sodium borohydride or methylmagnesium bromide, provides the corresponding hydroxy thiourea precursors in one pot, which can be easily transformed into *N*,*N*-disubstituted 4*H*-3,1-benzothiazin-2-amines on treatment with concentrated hydrobromic acid under mild conditions. The method is of use, because the starting materials are readily available and the manipulations are very easy, compared to the previous methods for the preparation of 4*H*-3,1-benzothiazin-2-amines[2] and related derivatives.[4]

3. Experimental

3.1. General

The melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded with a Perkin–Elmer Spectrum65 FTIR spectrophotometer. The ^1H NMR spectra were recorded in $CDCl_3$ using TMS as an internal reference with a Bruker Biospin AVANCE II 600 spectrometer operating at 600 MHz, a JEOL ECP500 FT NMR spectrometer operating at 500 MHz, or JEOL LA400FT NMR spectrometer operating at 400 MHz. The ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal reference with a Bruker Biospin AVANCE II 600 spectrometer operating at 150 MHz, a JEOL ECP500 FT NMR spectrometer operating at 125 MHz, or JEOL LA400FT NMR spectrometer operating at 100 MHz. Low-resolution MS spectra (EI, 70 eV, or CI) were measured by a JEOL JMS AX505

HA spectrometer. TLC was carried out on a Merck Kieselgel 60 PF_{254}. Column chromatography was performed using WAKO GEL C-200E. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

3.2. Starting materials

Aryl(2-isocyanophenyl)methanones were prepared by the method reported previously by us.[3,5] All other chemicals used in this study were commercially available.

3.2.1. Aryl(2-isothiocyanatophenyl)methanones ***1***. These compounds were prepared by reacting aryl(2-isocyanophenyl)methanones with sulfur in the presence of a catalytic amount of selenium under conditions reported by Fujiwara et al.[6]

*3.2.1.1. (2-Isothiocyanatophenyl)phenylmethanone (**1a**)*[7]. Yield: 94%; a yellow oil; R_f 0.49 (1:5 THF–hexane); IR (neat) 2099, 1662 cm^{-1}; ^1H NMR (500 MHz) δ 7.35–7.39 (m, 2H), 7.48–7.54 (m, 4H), 7.62 (t, J=7.3 Hz, 1H), 7.81 (dd, J=7.8, 1.4 Hz, 2H).

*3.2.1.2. (5-Chloro-2-isothiocyanatophenyl)phenylmethanone (**1b**)*[8]. Yield: 90%; a yellow solid; mp 63–64 °C (hexane); IR (KBr) 2076, 1667 cm^{-1}; ^1H NMR (500 MHz) δ 7.29 (d, J=8.6 Hz, 1H), 7.46–7.49 (m, 2H), 7.52 (t, J=7.4 Hz, 2H), 7.65 (t, J=7.4 Hz, 1H), 7.81 (dd, J=7.4, 1.1 Hz, 2H).

*3.2.1.3. (4-Chlorophenyl)(2-isothiocyanatophenyl)methanone (**1c**).* Yield: 82%; a pale-yellow solid; mp 73–74 °C (hexane–Et_2O); IR (KBr) 2137, 1661 cm^{-1}; ^1H NMR (400 MHz) δ 7.35–7.40 (m, 2H), 7.47–7.56 (m, 4H), 7.76 (d, J=8.3 Hz, 2H). Anal. Calcd for $C_{14}H_8ClNOS$: C, 61.43; H, 2.95; N, 5.12. Found: C, 61.32; H, 2.96; N, 5.12.

*3.2.1.4. (2-Isothiocyanatophenyl)(4-methoxyphenyl)methanone (**1d**).* Yield: 86%; a yellow oil; R_f 0.35 (1:5 AcOEt–hexane); IR (neat) 2086, 1656 cm^{-1}; ^1H NMR (500 MHz) δ 3.89 (s, 3H), 6.96 (d, J=9.2 Hz, 2H), 7.33 (d, J=7.4 Hz, 1H), 7.36 (td, J=7.4, 1.1 Hz, 1H), 7.46 (dd, J=7.4, 1.7 Hz, 1H), 7.49 (td, J=7.4, 1.7 Hz, 1H), 7.80 (d, J=9.2 Hz, 2H). Anal. Calcd for $C_{15}H_{11}NO_2S$: C, 66.89; H, 4.12; N, 5.20. Found: C, 66.63; H, 4.14; N, 5.03.

*3.2.1.5. (4,5-Dimethoxy-2-isothiocyanatophenyl)phenylmethanone (**1e**).* Yield: 72%; a yellow solid; mp 108–108.5 °C (hexane–Et_2O); IR (KBr) 2099, 1644 cm^{-1}; ^1H NMR (400 MHz) δ 3.89 (s, 3H), 3.95 (s, 3H), 6.78 (s, 1H), 7.03 (s, 1H), 7.50 (t, J=7.3 Hz, 2H), 7.61 (t, J=7.3 Hz, 1H), 7.79 (d, J=7.3 Hz, 2H). Anal. Calcd for $C_{16}H_{13}NO_3S$: C, 64.20; H, 4.38; N, 4.68. Found: C, 64.18; H, 4.44; N, 4.62.

3.3. General procedure for the preparation of thiourea derivatives 3 and 5

To a stirred solution of **1** (0.24 g, 1.0 mmol) in EtOH (for $NaBH_4$) or THF (for MeMgBr) (5 mL) at room temperature was added a secondary amine (1.0 mmol; for diamines 0.5 mmol) dropwise. After confirmation of complete consumption of **1** by TLC (silica gel) analyses, $NaBH_4$ or MeMgBr (2.0 mmol) was added and stirring was continued for 1 h at the same temperature. Saturated aqueous NH_4Cl (10 mL) was added and organic materials were extracted with AcOEt (3×10 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on silica gel to give **3** or **5**.

*3.3.1. 1,1-Diethyl-3-{2-[hydroxy(phenyl)methyl]phenyl}thiourea (**3a**).* A pale-yellow oil; R_f 0.42 (1:2 AcOEt–hexane); IR (neat) 3457, 1616, 1524, 1486, 1164 cm^{-1}; ^1H NMR (500 MHz) δ 1.20 (t, J=7.4 Hz, 6H), 3.55–3.64 (m, 5H), 5.95 (s, 1H), 7.23–7.24 (m, 3H), 7.28 (t, J=7.4 Hz, 1H), 7.32–7.37 (m, 5H), 7.53 (d, J=8.0 Hz, 1H). Anal. Calcd for $C_{18}H_{22}N_2OS$: C, 68.75; H, 7.05; N, 8.91. Found: C, 68.74; H, 7.05; N, 8.73.

*3.3.2. N-{2-[Hydroxy(phenyl)methyl]phenyl}piperidine-1-carbothioamide (**3b**).* A colorless oil; R_f 0.31 (1:2 AcOEt–hexane); IR (neat) 3431, 1619, 1527, 1491, 1157 cm^{-1}; ^1H NMR (500 MHz) δ 1.54–1.64 (m, 6H), 3.23 (br s, 1H), 3.64–3.66 (m, 4H), 5.92 (s, 1H), 7.20 (t, J=7.4 Hz, 1H), 7.26–7.28 (m, 3H), 7.31–7.35 (m, 5H), 7.42 (d, J=8.6 Hz, 1H). Anal. Calcd for $C_{19}H_{22}N_2OS$: C, 69.90; H, 6.79; N, 8.58. Found: C, 69.90; H, 6.81; N, 8.52.

*3.3.3. N-{2-[Hydroxy(phenyl)methyl]phenyl}morpholine-4-carbothioamide (**3c**).* A colorless oil; R_f 0.50 (2:1 AcOEt–hexane); IR (neat) 3425, 1620, 1524, 1490, 1159 cm^{-1}; ^1H NMR (500 MHz) δ 3.10 (br s, 1H), 3.59–3.63 (m, 8H), 5.91 (s, 1H), 7.22 (t, J=7.4 Hz, 1H), 7.28–7.30 (m, 2H), 7.34–7.37 (m, 5H), 7.50 (d, J=8.0 Hz, 1H), 7.67 (br s, 1H). Anal. Calcd for $C_{18}H_{20}N_2O_2S$: C, 65.83; H, 6.14; N, 8.53. Found: C, 65.78; H, 6.15; N, 8.52.

*3.3.4. N-[2-(1-Hydroxy-1-phenylethyl)phenyl]pyrrolidine-1-carbothioamide (**3d**).* A pale-yellow oil; R_f 0.15 (1:5 AcOEt–hexane); IR (neat) 3349, 1619, 1531, 1451, 1172 cm^{-1}; ^1H NMR (500 MHz) δ 1.87–1.88 (m, 4H), 1.91 (s, 3H), 3.27 (m, 1H), 3.54 (br s, 4H), 7.22 (t, J=7.4 Hz, 1H), 7.26–7.30 (m, 4H), 7.33 (d, J=7.6 Hz, 2H), 7.38 (td, J=7.6, 1.9 Hz, 1H), 7.59 (d, J=7.6 Hz, 1H), 7.69 (d, J=7.6 Hz, 1H). Anal. Calcd for $C_{19}H_{22}N_2OS$: C, 69.90; H, 6.79; N, 8.58. Found: C, 69.82; H, 6.73; N, 8.32.

*3.3.5. 3-[4-Chloro-2-hydroxy(phenyl)methyl]phenyl-1,1-diethylthiourea (**3e**).* A yellow oil; R_f 0.36 (1:2 AcOEt–hexane); IR (neat) 3289, 1613, 1521, 1489, 1159 cm^{-1}; ^1H NMR (500 MHz) δ 1.20 (t, J=6.9 Hz, 6H), 3.43 (br s, 1H), 3.57–3.64 (m, 4H), 5.89 (s, 1H), 7.20 (d, J=2.3 Hz, 1H), 7.25 (d, J=8.0 Hz, 1H), 7.29–7.38 (m, 6H), 7.52 (d, J=8.0 Hz, 1H). Anal. Calcd for $C_{18}H_{21}ClN_2OS$: C, 61.97; H, 6.07; N, 8.03. Found: C, 61.95; H, 6.09; N, 8.02.

*3.3.6. 1-[4-Chloro-2-hydroxy(phenyl)methyl]phenyl-3-methyl-3-phenylthiourea (**3f**).* A pale-yellow solid; mp 55–59 °C (hexane–Et_2O); IR (KBr) 3395, 1510, 1343, 1102 cm^{-1}; ^1H NMR (500 MHz) δ 2.05 (br s, 1H), 3.70 (s, 3H), 5.77 (s, 1H), 7.09 (d, J=2.3 Hz, 1H), 7.18–7.22 (m, 4H), 7.26–7.34 (m, 5H), 7.38 (tt, J=7.4, 1.1 Hz, 1H), 7.44 (t, J=7.4 Hz, 2H), 7.56 (d, J=8.6 Hz, 1H). $C_{21}H_{19}ClN_2OS$: C, 65.87; H, 5.00; N, 7.32. Found: C, 65.84; H, 5.04; N, 7.16.

*3.3.7. 1-{2-[(4-Chlorophenyl)hydroxymethyl]phenyl}-3,3-diethylthiourea (**3g**).* A pale-yellow oil; R_f 0.21 (1:3 AcOEt–hexane); IR (neat) 3307, 1524, 1352, 1091 cm^{-1}; ^1H NMR (400 MHz) δ 1.24 (t, J=7.3 Hz, 6H), 3.62–3.67 (m, 5H), 5.92 (s, 1H), 7.17–7.38 (m, 8H), 7.49 (d, J=7.8 Hz, 1H). Anal. Calcd for $C_{18}H_{21}ClN_2OS$: C, 61.97; H, 6.07; N, 8.03. Found: C, 61.75; H, 6.12; N, 8.11.

*3.3.8. N-{2-[(4-Chlorophenyl)hydroxymethyl]phenyl}piperidine-1-carbothioamide (**3h**).* A pale-yellow solid; mp 215–217 °C (hexane–THF); IR (KBr) 3333, 1522, 1328, 1088 cm^{-1}; ^1H NMR (400 MHz) δ 1.40–1.49 (m, 6H), 1.90 (s, 3H), 3.17 (br s, 1H), 3.38–3.54 (m, 4H), 7.20–7.41 (m, 7H), 7.54 (d, J=7.3 Hz, 1H), 7.70 (br s, 1H). Anal. Calcd for $C_{20}H_{23}ClN_2OS$: C, 64.07; H, 6.18; N, 7.47. Found: C, 64.07; H, 6.19; N, 7.46.

*3.3.9. 1,1-Diethyl-3-{2-[hydroxy(4-methoxyphenyl)methyl]phenyl}thiourea (**3i**).* A colorless viscous oil; R_f 0.32 (1:2 AcOEt–hexane); IR (neat) 3380, 1520, 1353, 1172 cm^{-1}; ^1H NMR (500 MHz) δ 1.21 (t, J=7.4 Hz, 6H), 3.38 (br s, 1H), 3.60–3.67 (m, 4H), 3.80 (s, 3H), 5.91 (s, 1H), 6.87 (d, J=8.6 Hz, 2H), 7.18–7.22 (m, 2H), 7.27 (d, J=8.6 Hz, 2H),

7.34 (ddd, *J*=8.0, 7.4, 2.3 Hz, 1H), 7.47 (br s, 1H), 7.63 (d, *J*=8.0 Hz, 1H). Anal. Calcd for $C_{19}H_{24}N_2O_2S$: C, 66.25; H, 7.02; N, 8.13. Found: C, 66.23; H, 7.06; N, 7.88.

*3.3.10. 1-{2-[Hydroxy(4-methoxyphenyl)methyl]phenyl}-3-methyl-3-phenylthiourea (**3j**).* A pale-yellow viscous oil; R_f 0.29 (1:3, AcOEt–hexane); IR (neat) 3325, 1512, 1345, 1173 cm^{-1}; ^1H NMR (500 MHz) δ 2.66 (br s, 1H), 3.72 (s, 3H), 3.81 (s, 3H), 5.78 (s, 1H), 6.83 (d, *J*=8.6 Hz, 2H), 7.10–7.20 (m, 6H), 7.31 (td, *J*=7.4, 1.1 Hz, 1H), 7.36–7.39 (m, 2H), 7.43 (dd, *J*=8.0, 7.4 Hz, 2H), 7.62 (d, *J*=8.0 Hz, 1H). Anal. Calcd for $C_{22}H_{22}N_2O_2S$: C, 69.81; H, 5.86; N, 7.40. Found: C, 69.70; H, 6.05; N, 7.16.

*3.3.11. 3-[2-Hydroxy(phenyl)methyl-4,5-dimethoxy]phenyl-1,1-diethylthiourea (**3k**).* A white solid; mp 54–56 °C (hexane–Et_2O); IR (KBr) 3418, 1615, 1520, 1354, 1222 cm^{-1}; ^1H NMR (400 MHz) δ 1.21 (t, *J*=7.3 Hz, 6H), 3.58 (br, 4H), 3.74 (br s, 1H), 3.81 (s, 3H), 3.87 (s, 3H), 5.88 (s, 1H), 6.78 (s, 1H), 6.85 (s, 1H), 6.94 (s, 1H), 7.25–7.38 (m, 5H). Anal. Calcd for $C_{20}H_{26}N_2O_3S$: C, 64.14; H, 7.00; N, 7.48. Found: C, 63.96; H, 6.98; N, 7.45.

*3.3.12. 1,1′-(Ethane-1,2-diyl)bis(3-{2-[hydroxy(phenyl)methyl]phenyl}-1-methylthiourea) (**5a**).* A mixture of diastereomers (ca. 1:1); a white solid; R_f 0.26 (1:1, AcOEt–hexane); mp 119–131 °C; IR (KBr) 3425, 3234, 1533, 1344 cm^{-1}; ^1H NMR (500 MHz) δ 1.68 (br s, 2H), 3.11–3.28 (m, 10H), 5.92 (s, 1H), 5.94 (s, 1H), 6.98–7.59 (m, 20H). Anal. Calcd for $C_{32}H_{34}N_4O_2S_2$: C, 67.34; H, 6.00; N, 9.82. Found: C, 67.31; H, 6.00; N, 9.80.

*3.3.13. 1,1′-(Propane-1,3-diyl)bis(3-{2-[hydroxy(phenyl)methyl]-4,5-dimethoxyphenyl}-1-methylthiourea) (**5b**).* A mixture of diastereomers (ca. 1:1); a white solid; R_f 0.39 (AcOEt); mp 90–125 °C; IR (KBr) 3312, 1611, 1523, 1341 cm^{-1}; ^1H NMR (500 MHz) δ 1.56 (br s, 2H), 2.04 (br s, 2H), 3.03 (s, 6H), 3.79 (s, 6H), 3.82 (s, 6H), 3.85–3.90 (m, 4H), 5.85 (s, 2H), 6.71 (s, 1H), 6.72 (s, 1H), 6.99 (s, 1H), 7.00 (s, 1H), 7.25–7.36 (m, 12H). Anal. Calcd for $C_{37}H_{44}N_4O_6S_2$: C, 63.04; H, 6.29; N, 7.95. Found: C, 62.99; H, 6.47; N, 7.90.

3.4. Typical procedure for the preparation of *N,N*-disubstituted 4*H*-3,1-benzothiazin-2-amine derivatives 4 and 6

*3.4.1. N,N-Diethyl-4-phenyl-4H-3,1-benzothiazin-2-amine (**4a**).* To a stirred solution of **2a** (0.10 g, 0.32 mmol) in MeCN (3 mL) was added concentrated HBr (0.32 mmol, 55 mg). Stirring was continued at the same temperature until TLC analyses had revealed complete consumption of the starting material. Saturated aqueous $NaHCO_3$ (10 mL) was added, and the organic solvent was removed by evaporation. The resulting mixture was extracted with AcOEt (3×10 mL) and the combined extracts were washed with brine, dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on silica gel (1:10 AcOEt–hexane) to give **4a** (80 mg, 85%); colorless crystals; mp 96–99 °C (hexane–THF); IR (KBr) 1602, 1543 cm^{-1}; ^1H NMR (500 MHz) δ 1.13 (t, *J*=7.4 Hz, 6H), 3.52–3.63 (m, 4H), 5.21 (s, 1H), 6.89 (dd, *J*=7.4, 1.7 Hz, 1H), 6.94 (td, *J*=7.4, 1.1 Hz, 1H), 7.17 (dd, *J*=8.0, 1.1 Hz, 1H), 7.23–7.30 (m, 6H); ^{13}C NMR (125 MHz) δ 14.04, 43.40, 47.35, 122.55, 122.57, 124.75, 126.28, 127.55, 128.04, 128.27, 128.55, 140.59, 146.57, 153.28; MS *m*/*z* 296 (M^+, 100). Anal. Calcd for $C_{18}H_{20}N_2S$: C, 72.93; H, 6.80; N, 9.45. Found: C, 72.70; H, 6.81; N, 9.41.

*3.4.2. 4-Phenyl-2-(piperidin-1-yl)-4H-3,1-benzothiazine (**4b**).* A white solid; mp 59–62 °C (hexane); IR (KBr) 1602, 1553 cm^{-1}; ^1H NMR (500 MHz) δ 1.46–1.63 (m, 6H), 3.67–3.74 (m, 4H), 5.23 (s, 1H), 6.90 (d, *J*=7.4 Hz, 1H), 6.97 (t, *J*=7.4 Hz, 1H), 7.18 (d, *J*=8.0 Hz, 1H), 7.24–7.29 (m, 6H); ^{13}C NMR (125 MHz) δ 24.98, 25.93, 47.35, 47.80, 122.59, 122.97, 124.84, 126.33, 127.56, 128.01, 128.28, 128.55, 140.59, 146.31, 154.37; MS *m*/*z* 308 (M^+, 100). Anal. Calcd for $C_{19}H_{20}N_2S$: C, 73.99; H, 6.54; N, 9.08. Found: C, 73.92; H, 6.74; N, 9.07.

*3.4.3. 2-(Morpholin-4-yl)-4-phenyl-4H-3,1-benzothiazine (**4c**).* A colorless oil; R_f 0.34 (1:5, AcOEt–hexane); IR (neat) 1601, 1551 cm^{-1}; ^1H NMR (500 MHz) δ 3.61–3.78 (m, 8H), 5.26 (s, 1H), 6.92 (d, *J*=7.4 Hz, 1H), 7.01 (td, *J*=7.4, 1.1 Hz, 1H), 7.19 (dd, *J*=7.8, 1.1 Hz, 1H), 7.22–7.32 (m, 6H); ^{13}C NMR (125 MHz) δ 47.18, 47.30, 66.71, 122.54, 123.73, 125.04, 126.49, 127.75, 127.94, 128.45, 128.65, 140.34, 145.61, 154.80; MS *m*/*z* 310 (M^+, 100). Anal. Calcd for $C_{18}H_{18}N_2OS$: C, 69.65; H, 5.84; N, 9.02. Found: C, 69.60; H, 5.94; N, 8.75.

*3.4.4. 4-Methyl-4-phenyl-2-(pyrrolidin-1-yl)-4H-3,1-benzothiazine (**4d**).* A colorless oil; R_f 0.21 (1:10 AcOEt–hexane); IR (neat) 1601, 1551 cm^{-1}; ^1H NMR (400 MHz) δ 1.89–1.92 (m, 4H), 1.99 (s, 3H), 3.59 (br s, 4H), 6.95–6.96 (m, 2H), 7.17–7.29 (m, 5H), 7.42 (dd, *J*=7.3, 1.5 Hz, 2H); ^{13}C NMR (125 MHz) δ 24.99, 28.25, 47.58, 52.08, 122.51, 124.05, 125.10, 127.19, 127.60, 127.94, 128.01, 128.56, 144.57, 146.16, 153.22; MS *m*/*z* 308 (M^+, 100). Anal. Calcd for $C_{19}H_{20}N_2S$: C, 73.99; H, 6.54; N, 9.08. Found: C, 73.92; H, 6.57; N, 9.02.

*3.4.5. 6-Chloro-N,N-diethyl-4-phenyl-4H-3,1-benzothiazin-2-amine (**4e**).* A white solid; mp 91–93 °C (hexane); IR (KBr) 1597, 1551 cm^{-1}; ^1H NMR (500 MHz) δ 1.13 (t, *J*=6.9 Hz, 6H), 3.51–3.63 (m, 4H), 5.15 (s, 1H), 6.85 (d, *J*=2.3 Hz, 1H), 7.09 (d, *J*=8.6 Hz, 1H), 7.19 (dd, *J*=8.6, 2.3 Hz, 1H), 7.23–7.33 (m, 5H); ^{13}C NMR (125 MHz) δ 14.01, 43.46, 47.11, 124.07, 125.91, 126.02, 127.08, 127.91, 127.99, 128.22, 128.73, 139.63, 145.34, 153.58; MS *m*/*z* 330 (M^+, 100). Anal. Calcd for $C_{18}H_{19}ClN_2S$: C, 65.34; H, 5.79; N, 8.47. Found: C, 65.22; H, 5.83; N, 8.45.

*3.4.6. 6-Chloro-N-methyl-N,4-diphenyl-4H-3,1-benzothiazin-2-amine (**4f**).* A white solid; mp 85–88 °C (hexane); IR (KBr) 1597, 1545 cm^{-1}; ^1H NMR (500 MHz) δ 3.52 (s, 3H), 5.09 (s, 1H), 6.87 (d, *J*=2.3 Hz, 1H), 7.03–7.05 (m, 2H), 7.17 (dd, *J*=8.6, 2.3 Hz, 1H), 7.21–7.33 (m, 9H); ^{13}C NMR (125 MHz) δ 39.66, 47.60, 124.57, 126.28, 126.32, 127.29, 127.73, 127.92, 128.09, 128.27, 128.32, 128.68, 129.14, 139.20, 144.65, 144.73, 154.66; MS *m*/*z* 364 (M^+, 100). Anal. Calcd for $C_{21}H_{17}ClN_2S$: C, 69.12; H, 4.70; N, 9.72. Found: C, 68.95; H, 4.81; N, 9.64.

*3.4.7. 4-(4-Chlorophenyl)-N,N-diethyl-4H-3,1-benzothiazin-2-amine (**4g**).* A colorless oil; R_f 0.49 (1:10 AcOEt–hexane); IR (neat) 1602, 1550 cm^{-1}; ^1H NMR (400 MHz) δ 1.12 (t, *J*=7.3 Hz, 6H), 3.56 (q, *J*=7.3 Hz, 4H), 5.16 (s, 1H), 6.90 (d, *J*=7.3 Hz, 1H), 6.96 (t, *J*=7.3 Hz, 1H), 7.14–7.29 (m, 6H); ^{13}C NMR (100 MHz) δ 14.05, 43.43, 46.57, 121.73, 122.68, 124.92, 126.31, 128.51, 128.65, 129.25, 133.26, 139.53, 146.43, 152.62; MS *m*/*z* 330 (M^+, 100). Anal. Calcd for $C_{18}H_{19}ClN_2S$: C, 65.34; H, 5.79; N, 8.47. Found: C, 65.23; H, 5.87; N, 8.40.

*3.4.8. 4-(4-Chlorophenyl)-4-methyl-2-(piperidin-1-yl)-4H-3,1-benzothiazine (**4h**).* A white solid; mp 99–101 °C (hexane); IR (KBr) 1600, 1547 cm^{-1}; ^1H NMR (600 MHz) δ 1.49–1.54 (m, 4H), 1.97 (s, 3H), 1.58–1.64 (m, 2H), 3.68–3.70 (m, 4H), 7.04 (ddd, *J*=7.7, 7.1, 1.3 Hz, 1H), 7.08 (dd, *J*=7.7, 1.6 Hz, 1H), 7.18 (dd, *J*=7.9, 1.3 Hz, 1H), 7.20 (d, *J*=8.8 Hz, 2H), 7.26–7.29 (m, 3H); ^{13}C NMR (150 MHz) δ 25.01, 26.07, 27.93, 47.73, 51.55, 123.06, 123.49, 125.27, 128.07, 128.16, 128.37, 128.69, 132.92, 143.61, 145.20, 154.93; MS *m*/*z* 356 (M^+, 100). Anal. Calcd for $C_{20}H_{21}ClN_2S$: C, 67.30; H, 5.93; N, 7.85. Found: C, 67.26; H, 5.99; N, 7.92.

*3.4.9. N,N-Diethyl-4-(4-methoxyphenyl)-4H-3,1-benzothiazin-2-amine (**4i**).* A colorless oil; R_f 0.47 (1:5 AcOEt–hexane); IR (neat)

1608, 1549 cm^{-1}; ^1H NMR (400 MHz) δ 1.14 (t, J=7.3 Hz, 6H), 3.51–3.65 (m, 4H), 3.78 (s, 3H), 5.18 (s, 1H), 6.82 (d, J=8.8 Hz, 2H), 6.88 (d, J=7.3 Hz, 1H), 6.94 (t, J=7.3 Hz, 1H), 7.16–7.25 (m, 4H); ^{13}C NMR (125 MHz) δ 14.06, 43.36, 46.87, 55.26, 113.94, 122.54, 123.03, 124.71, 126.12, 128.16, 129.28, 132.44, 146.59, 153.57, 159.01; MS m/z 326 (M^+, 100). Anal. Calcd for $C_{19}H_{22}N_2OS$: C, 69.90; H, 6.79; N, 8.58. Found: C, 69.82; H, 6.99; N, 8.47.

*3.4.10. 4-(4-Methoxyphenyl)-N-methyl-N-phenyl-4H-3,1-benzothiazin-2-amine (**4j**).* A colorless oil; R_f 0.42 (1:4 AcOEt–hexane); IR (neat) 1607, 1547 cm^{-1}; ^1H NMR (400 MHz) δ 3.52 (s, 3H), 3.77 (s, 3H), 5.12 (s, 1H), 6.80 (d, J=8.8 Hz, 2H), 6.89 (d, J=7.8 Hz, 1H), 6.99–7.11 (m, 5H), 7.23–7.33 (m, 5H); ^{13}C NMR (100 MHz) δ 39.62, 47.32, 55.26, 113.85, 123.43, 123.58, 125.10, 126.39, 127.00, 127.74, 128.23, 129.03, 129.32, 132.05, 144.80, 145.95, 154.52, 159.00; MS m/z 360 (M^+, 100). Anal. Calcd for $C_{22}H_{20}N_2OS$: C, 73.30; H, 5.59; N, 7.77. Found: C, 73.10; H, 5.75; N, 7.70.

*3.4.11. N,N-Diethyl-6,7-dimethoxy-4-phenyl-4H-3,1-benzothiazin-2-amine (**4k**).* A white solid; mp 104–106 °C (hexane–Et_2O); IR (KBr) 1612, 1560 cm^{-1}; ^1H NMR (400 MHz) δ 1.11 (t, J=7.3 Hz, 6H), 3.51–3.58 (m, 4H), 3.74 (s, 3H), 3.91 (s, 3H), 5.15 (s, 1H), 6.44 (s, 1H), 6.78 (s, 1H), 7.21–7.28 (m, 5H); ^{13}C NMR (100 MHz) δ 14.00, 43.27, 47.08, 55.85, 56.21, 108.38, 109.86, 113.20, 127.48, 127.83, 128.51, 140.73, 141.17, 144.73, 149.06, 152.17; MS m/z 356 (M^+, 100). Anal. Calcd for $C_{20}H_{24}N_2O_2S$: C, 67.38; H, 6.79; N, 7.86. Found: C, 67.35; H, 6.91; N, 7.79.

*3.4.12. N,N′-Dimethyl-N,N′-bis(4-phenyl-4H-3,1-benzothiazin-2-yl) ethane-1,2-diamine (**6a**).* A mixture of diastereomers (ca. 1:1); a white solid; R_f 0.41 (1:3 AcOEt–hexane); mp 143–172 °C; IR (KBr) 1602, 1549 cm^{-1}; ^1H NMR (500 MHz) δ 2.98 (s, 3H), 3.00 (s, 3H), 3.67 (br s, 4H), 5.19 (s, 2H), 6.90 (d, J=7.4 Hz, 1H), 6.91 (d, J=7.4 Hz, 1H), 6.97 (t, J=7.4 Hz, 2H), 7.16–7.18 (m, 6H), 7.20–7.27 (m, 8H); ^{13}C NMR (125 MHz) δ 30.30, 37.46, 47.17, 121.53, 121.94, 122.01, 123.03, 124.86, 124.88, 126.48, 126.50, 127.60, 127.97, 128.01, 128.40, 128.56, 140.50, 140.62, 146.21, 146.25, 153.91; MS (CI) m/z 535 ($[M+1]^+$, 100). Anal. Calcd for $C_{32}H_{30}N_4S_2$: C, 71.87; H, 5.65; N, 10.48. Found: C, 71.70; H, 5.65; N, 10.18.

*3.4.13. N,N′-Bis(6,7-dimethoxy-4-phenyl-4H-benzo[d][1,3]thiazin-2-yl)-N,N′-dimethylpropane-1,3-diamine (**6b**).* A mixture of diastereomers (ca. 1:1); a pale-yellow viscous oil; R_f 0.39 (1:2 AcOEt–hexane); IR (neat) 1609, 1557 cm^{-1}; ^1H NMR (400 MHz) δ 1.57–1.60 (m, 2H), 3.01 (s, 6H), 3.21–3.30 (m, 4H), 3.75 (s, 6H), 3.91 (s, 6H), 5.15 (s, 2H), 6.46 (s, 1H), 6.47 (s, 1H), 6.79 (s, 1H), 6.80 (s, 1H), 7.14–7.21 (m, 10H); ^{13}C NMR (125 MHz) δ 14.18, 21.03, 26.43, 26.46, 47.04, 48.53, 55.88, 56.18, 60.37, 108.50, 109.87, 112.66, 127.52, 127.70, 128.53, 140.42, 141.23, 141.27, 145.04, 149.11, 152.76; MS (CI) m/z 669 ($[M+1]^+$, 100). Anal. Calcd for $C_{37}H_{40}N_4O_4S_2$: C, 66.44; H, 6.03; N, 8.38. Found: C, 66.36; H, 6.26; N, 8.34.

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