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ONE-POT SYNTHESIS OF BENZOTHIAZOL-2-AMINES BY CYCLIZATION OF THE ADDUCTS BETWEEN 2-IODOPHENYL ISOTHIOCYANATES AND AMINES UNDER METAL-FREE CONDITIONS

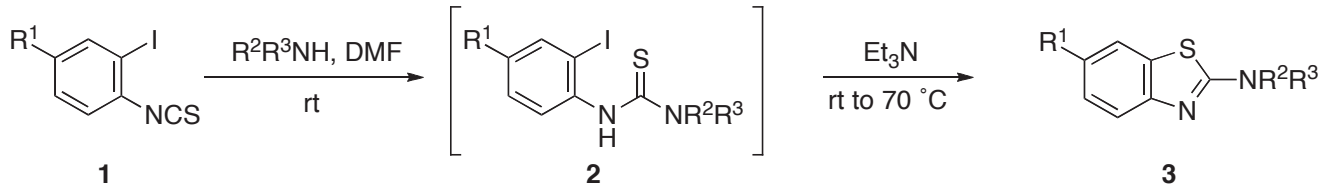
Kazuhiro Kobayashi,* Akihiro Kobayashi, Kazuya Murahashi, and Shuhei Fukamachi

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 – A convenient one-pot procedure for the preparation of *N*-substituted and *N,N*-disubstituted benzothiazol-2-amines under metal-free conditions has been developed, which employs the reaction of 2-iodophenyl isothiocyanates with primary and secondary amines followed by cyclization of the resulting thiourea precursors on treatment with triethylamine under relatively mild reaction conditions (< 70 ˚C). The reactions using diamines, such as ethylenediamines or trimethylenediamine, under similar conditions, albeit at higher temperature (130 ˚C), have proved to enable us to obtain *N,N'*-bis(benzothiazol-2-yl)ethane(or propane)diamines.

Benzothiazol-2-amine derivatives are an important class of heterocycles, because a number of molecules having this skeleton have been shown to exhibit a variety of biological activities.[1] Therefore, there are many procedures available to prepare this type of compounds.[2,3] The most facile method for the preparation of these derivatives is based on the substitution of 2-chlorobenzothiazole with amines.[4] Recently, Batey's group has demonstrated that the synthesis of *N*-substituted and *N,N*-disubstituted benzothiazol-2-amines can be achieved efficiently by using a transition metal [$Pd(PPh_3)_4$ or CuI] catalyzed intramolecular cyclization of 1-(di)alkylamino-3-(2-iodo(or bromo)phenyl)thioureas, prepared mainly by the addition of 2-iodo(or bromo)phenyl isothiocyanates with primary and secondary amines, at a relative higher temperature (80 ˚C).[2a] Later, one-pot preparation of *N*-arylbenzothiazol-2-amines by CuBr catalyzed cyclization of the adducts between 2-iodobenzenamines and aryl isothiocyanates has been reported Li *et al*.[2d] Now we wish to describe a convenient procedure for the synthesis of *N*-substituted and *N,N*-disubstituted benzothiazol-2-amines (**3**) from 2-iodophenyl isothiocyanates (**1**) and primary or

secondary amines under metal-free[5] and mild conditions.[6] After completion of this work, we were aware of a report by Liu *et al*., which demonstrated that benzothiazol-2-amine derivatives could be obtained by treating *N'*-substituted-*N*-(2-halophenyl)thioureas with two equivalents of Cs_2CO_3 in dioxane at 130 °C.[7] Our new procedure has been applied to one-pot preparation of *N,N'*-bis(benzothiazol-2-yl)ethane(or propane)diamines (**5**) by using ethylenediamines and trimethylenediamine. *N,N'*-Bis(benzothiazol-2-yl)ethanediamines have recently be prepared by the reaction of 2-chlorobenzothiazoles with ethylenediamines and some of these derivatives have been reported to exhibit high binding affinity to β-amiloyd fibrils.[8]



Scheme 1

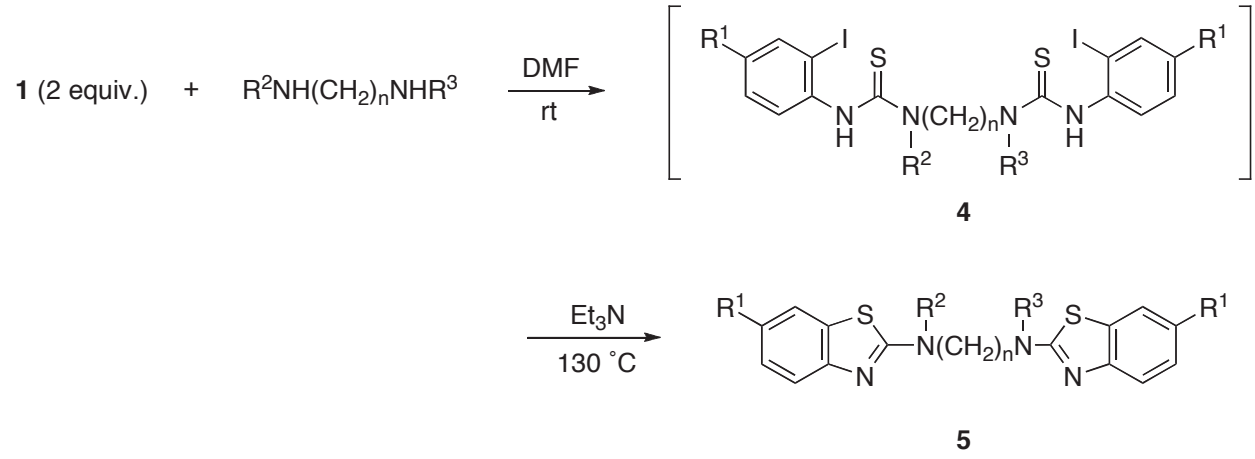
Table 1. Preparation of Benzothiazol-2-amine Derivatives (**3**)

Entry	**1**	Amine	Temp	Time	**3**	Yield/%[a]
1	**1a** (R^1 = H)	$BnNH_2$	rt	10 min	**3a**	96
2	**1a**	pyrrolidine	rt	10 min	**3b**	99
3	**1a**	BnNH(*i*-Pr)	rt	15 min	**3c**	91
4	**1b** (R^1 = Cl)	$PhNH_2$	70 °C	6 h	**3d**	76
5	**1b**	$HO(CH_2)_2NHMe$	70 °C	30 min	**3e**	74
6	**1c** (R^1 = Br)	Et_2NH	50 °C	50 min	**3f**	92
7	**1c**	morpholine	50 °C	1 h	**3g**	86

[a] Yields of isolated products.

The starting 2-iodophenyl isothiocyanates (**1**) were readily available; 2-iodophenyl isothiocyanate (**1a**) was commercially available and 4-chloro- (**1b**) and 4-bromo-2-iodophenyl isothiocyanates (**1c**) could be prepared from the respective commercially available 2-iodoanilines in good yields utilizing previously reported procedures[9-11] as described in EXPERIMENTAL. Conversion of **1** into the desired *N*-substituted and *N,N*-disubstituted benzothiazol-2-amines (**3**) was carried out according to the procedure illustrated in Scheme 1. Thus, compounds (**1**) were allowed to react with primary and secondary amines in DMF at room temperature to result in the immediate formation of the corresponding 1-(2-iodophenyl)thiourea derivatives (**2**). On treatment with an equimolar amount of Et_3N and an additional stirring of the reaction mixture at the temperatures indicated in Table 1, these precursors cleanly underwent cyclization by intramolecular substitution of the sulfur atom of the thiourea moiety for the 2-iodo group to provide, after usual aqueous workup and the subsequent purification of the crude products by recrystallization or

column chromatography on silica gel, the desired benzothiazol-2-amines (**3**) in generally good yields as summarized in Table 1. It indicates that the use of an aromatic amine, such as aniline, requires a rather extended reaction time (Entry 4). The ease of cyclization in the present method compared to other metal-free methods may be ascribed to the use of DMF as a solvent.



Scheme 2

Table 2. Preparation of *N,N'*-Bis(benzthiazol-2-yl)alkanediamines (**5**)

Entry	**1**	Diamine	Time/h	**5**	Yield/%[a]
1	**1a**	$MeNH(CH_2)_2NHMe$	3	**5a**	66
2	**1a**	$NH_2(CH_2)_3NH_2$	1	**5b**	51
3	**1b**	$MeNH(CH_2)_2NH_2$	2	**5c**	53
4	**1b**	$EtNH(CH_2)_2NHEt$	4	**5d**	72
5	**1b**	$NH_2(CH_2)_3NH_2$	3	**5e**	45
6	**1c**	$EtNH(CH_2)_2NHEt$	2	**5f**	71

[a] Yields of isolated products.

With the above-mentioned results in hand, the reaction of 2-iodophenyl isothiocyanates (**1**) with diamines, such as ethylenediamines and trimethylenediamine, was then explored in order to develop a procedure obtaining *N,N'*-bis(benzothiazol-2-yl)ethane(or propane)diamines (**5**). The initial experiment using 2-iodophenyl isothiocyanate (**1a**) (two molar amounts) and *N,N'*-dimethylethylenediamine was conducted under similar conditions as for the preparation of (**3**). Unfortunately, however, the cyclization of two thiazole rings producing the desired product (**5a**) could not be accomplished even by heating at 70˚, while the addition of the diamine to isothiocyanate giving the adduct **4a** occurred immediately at room temperature. However, we were delighted to observe that, when the mixtures of **1** and diamines were heated at 130˚ as depicted in Scheme 2, the desired products (**5**) could be obtained in moderate to fair yields as summarized in Table 2. It should be noted that an attempted use of *p*-phenylenediamine as a diamine under similar conditions resulted in the formation of a complicated mixture of the products.

In conclusion, the results detailed herein demonstrate that *N*-substituted or *N*,*N*-disubstituted benzothiazol-2-amines (**3**) can be conveniently prepared in one pot from 2-iodophenyl isothiocyanates and primary or secondary amines. The present method may be of value in organic synthesis because of its advantages over previous similar methods: i) unnecessity of any metal catalysts, ii) mild reaction conditions, iii) use of a cheap organic base, iv) simplicity of the procedure, v) easy availability of the starting materials, and vi) applicability to the synthesis of *N*,*N*'-bis(benzothiazol-2-yl)alkane-1,ω-diamines.

EXPERIMENTAL

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 ^{1}H NMR spectra were recorded in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz. The ^{13}C NMR spectra were recorded using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. Low-resolution MS spectra (EI, 70 eV) 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.

Starting Materials. *N*-(4-Chloro-2-iodophenyl)formamide was prepared by the procedure reported previously by us.[10] All other chemicals used in this study were commercially available.

***N*-(4-Bromo-2-iodophenyl)formamide.** This compound was prepared by *N*-formylation of 4-bromo-2-iodoaniline with HCO_2H under the conditions reported previously by us;[10] yield: 73%; a pale-yellow solid; mp 158–160 °C (hexane–AcOEt); IR (KBr) 3229, 1654 cm^{-1}; ^{1}H NMR δ 7.08–8.64 (m, 5H). Anal. Calcd for C_7H_5BrINO: C, 25.80; H, 1.55; N, 4.30. Found: C, 25.50; H, 1.54; N 4.19.

1-Chloro-3-iodo-4-isothiocyanatobenzene (**1b**). *N*-(4-Chloro-2-iodophenyl)formamide (1.8 g, 6.5 mmol) was dissolved in THF (20 mL) and to this solution at 0 °C was added Et_3N (4.6 g, 46 mmol) and $POCl_3$ (1.4 g, 9.2 mmol) under stirring.[11] After 5 min, saturated aqueous $NaHCO_3$ (20 mL) was added and the mixture was extracted with Et_2O (3 × 20 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (20 mL) and then brine (20 mL), and dried over anhydrous K_2CO_3. Evaporation of the solvent gave a crude 1-chloro-3-iodo-4-isocyanobenzene (1.5 g) as a yellow solid; mp 85–88 °C (decomp); IR (KBr) 2129 cm^{-1}; ^{1}H NMR δ 7.34 (d, *J* = 8.7 Hz, 1H), 7.37 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.89 (d, *J* = 1.8 Hz, 1H). This isocyanide was used in the next step without any purification. Thus, a mixture of this isocyanide in THF (15 mL) containing Et_3N (1.4 g, 14 mmol), sulfur (21 mg, 6.7 mmol), and selenium (13 mg, 0.17 mmol) was stirred for 2 h at rt.[9] After concentration of the mixture by evaporation, the residue was subjected to column chromatography on silica gel (hexane) to give the crude product, which was purified by recrystallization to give pure **1b** (1.4 g, 89%); colorless needles; mp 65–67 °C

(pentane). IR (KBr) 2085 cm^{-1}; ^1H NMR δ 7.18 (d, *J* = 8.7 Hz, 1H), 7.31 (dd, *J* = 8.7, 2.3 Hz, 1 H), 7.80 (d, *J* = 2.3 Hz, 1H). Anal. Calcd for C_7H_3ClINS: C, 28.45; H, 1.02; N, 4.74. Found: C, 28.38; H, 1.08; N, 4.78.

1-Bromo-3-iodo-4-isothiocyanatobenzene (**1c**). This compound was prepared from *N*-(4-bromo-2-iodophenyl)formamide in a manner similar to that described for the preparation of **1b**, via 1-bromo-3-iodo-4-isocyanobenzene [a pale-yellow solid; mp 90–95 °C; IR (KBr) 2128 cm^{-1}; ^1H NMR δ 7.28 (d, *J* = 8.2 Hz, 1H), 7.52 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.05 (*d*, *J* = 1.8 Hz, 1H)], in 88% yield. A white solid; mp 81–84 °C (hexane); IR (KBr): 2083 cm^{-1}; ^1H NMR δ 7.12 (d, *J* = 8.2 Hz, 1H), 7.45 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.95 (d, *J* = 1.8 Hz, 1H). Anal. Calcd for C_7H_3BrINS: C, 24.73; H, 0.89; N, 4.12. Found: C, 24.67; H, 0.92; N, 3.86.

General Procedure for the Preparation of Benzothiazol-2-amines (3). To a stirred solution of **1** (1.0 mmol) in DMF (5 mL) at rt was added an amine (1.0 mmol). After 5 min, Et_3N (0.10 g, 1.0 mmol) was added and the mixture was then stirred under the conditions indicated in Table 1. Water (20 mL) was added and the mixture was extracted with AcOEt (3 × 10 mL). The combined extracts were washed with water (3 × 10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by recrystallization or column chromatography on silica gel to give **3**.

***N*-Benzylbenzothiazol-2-amine (3a):** A white solid; mp 165–167 °C (hexane–CH_2Cl_2) (lit.,[12] mp 166–167 °C). The spectral (IR, ^1H NMR, and ^{13}C NMR) data were identical to those reported previously.[4]

2-(Pyrrolidin-1-yl)benzothiazole (3b): a white solid; mp 99–102 °C (hexane-CH_2Cl_2) (lit.,[3a] mp 101–103 °C). The ^1H NMR data were identical to those reported previously.[3a]

***N*-Benzyl-*N*-isopropylbenzothiazol-2-amine (3c):** a colorless oil. R_f 0.55 (THF–hexane 1:4); IR (neat) 1595, 1526 cm^{-1}; ^1H NMR δ 1.27 (d, *J* = 6.9 Hz, 6H), 4.65 (sept, *J* = 6.9, 1H), 4.71 (s, 2H), 7.04 (t, *J* = 7.3, 1H), 7.22–7.35 (m, 6H), 7.55 (dd, *J* = 8.2, 1.4 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 20.38, 49.40, 52.33, 118.85, 120.49, 120.92, 125.80, 126.78, 127.10, 128.50, 130.64, 138.30, 152.80, 168.78; MS *m*/*z* 282 (47, M^+), 239 (100). Anal. Calcd for $C_{17}H_{18}N_2S$: C, 72.30; H, 6.42; N, 9.92. Found: C, 72.13; H, 6.47; N, 9.86.

6-Chloro-*N*-phenylbenzothiazol-2-amine (3d): a white solid; mp 196–198 °C (hexane–Et_2O) (lit.,[13] mp 198–200 °C); IR (KBr) 3237, 1624 1603, 1568 cm^{-1}; ^1H NMR δ 7.18 (t, *J* = 7.3 Hz, 1H), 7.29 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.41 (dd, *J* = 8.2, 7.3 Hz, 2H), 7.48–7.50 (*m*, 3H), 7.59 (d, *J* = 1.8, Hz, 1H), 8.08 (br s, 1H).

2-[*N*-(6-Chlorobenzothiazol-2-yl)-*N*-methylamino]ethanol (3e): a white solid; mp 111–113 °C (hexane–Et_2O); IR (KBr) 3374, 1597, 1541 cm^{-1}; ^1H NMR δ 3.22 (s, 3H), 3.63 (br s, 1H), 3.78 (t, *J* = 5.0 Hz, 2H), 3.92–3.95 (m, 2H), 7.24 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 1H), 7.55 (d, *J* = 1.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 40.21, 55.81, 61.46, 119.36, 120.31, 126.32, 126.49, 131.86, 151.02, 169.64; MS *m*/*z* 242 (100, M^+). Anal. Calcd for $C_{10}H_{11}ClN_2OS$: C, 49.48; H, 4.57; N, 11.54. Found: C, 49.31; H, 4.61; N, 11.32.

6-Bromo-*N*,*N*-diethylbenzothiazole-2-amine (3f): a pale-yellow solid; mp 43–44 °C (hexane); IR (KBr)

1595, 1539 cm^{-1}; ^1H NMR δ 1.28 (t, *J* = 7.3 Hz, 6H), 3.56 (q, *J* = 7.3 Hz, 4H), 7.35 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.67 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.80, 45.46, 112.79, 119.59, 122.91, 128.92, 132.34, 152.31, 167.41; MS *m/z* 284 (33, M^+), 255 (100). Anal. Calcd for $C_{11}H_{13}BrN_2S$: C, 46.32; H, 4.59; N 9.82. Found: C, 46.46; H, 4.60; N 9.85.

6-Bromo-2-(morpholin-4-yl)benzothiazole (3g): a beige solid; mp 161–163 ˚C (hexane); IR (KBr) 1591, 1535 cm^{-1}; ^1H NMR δ 3.61 (t, *J* = 5.0 Hz, 4H); 3.83 (t, *J* = 5.0 Hz, 4H), 7.40 (s, 2H), 7.72 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 48.42, 66.16, 113.95, 120.38, 123.23, 129.31, 132.23, 151.51, 168.99; MS *m/z* 298 (100, M^+). Anal. Calcd for $C_{11}H_{11}BrN_2OS$: C, 44.16; H, 3.71; N, 9.36. Found: C, 43.94; H, 3.71; N, 9.31.

General Procedure for the Preparation of *N,N'*-Bis(benzothiazol-2-yl)alkane-1,ω-diamines (5). To a stirred solution of **1** (1.0 mmol) in DMF (4 mL) was added a diamine (0.50 mmol) at rt. After 5 min, Et_3N (0.11 g, 1.1 mmol) was added and the mixture was heated at 130 ˚C for the time indicated in Table 2 under stirring. Water (15 mL) was added and the mixture was extracted with AcOEt (3 × 10 mL). The combined extracts were washed with H_2O (3 × 10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. After evaporation of the solvent the residue was purified by recrystallization or column chromatography on silica gel to give **5**.

***N,N'*-Bis(benzothiazol-2-yl)-*N,N'*-dimethylethane-1,2-diamines (5a):** colorless needles; mp 173–175 ˚C (hexane–CH_2Cl_2). The ^1H-NMR data for this product were identical to those reported previously.[7]

***N,N'*-Bis(benzothiazol-2-yl)propane-1,3-diamines (5b):** a white solid; mp 188–190 ˚C (hexane–$CHCl_3$); IR (KBr) 3225, 1610, 1574, 1433 cm^{-1}; ^1H NMR δ 2.01 (quint, *J* = 6.0 Hz, 2H), 3.65 (t, *J* = 6.0 Hz, 4H), 6.22 (s, 2H), 7.09 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 2H), 7.30 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 2H), 7.57 (dd, *J* = 7.8, 1.4 Hz, 2H), 7.58 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 29.80, 41.64, 118.91, 120.77, 121.72, 125.97, 130.38, 152.32, 167.16; MS *m/z* 340 (38, M^+), 191 (100). Anal. Calcd for $C_{17}H_{16}N_4S_2$: C, 59.97; H, 4.74; N, 16.46. Found: C, 59.86; H, 4.80; N, 16.32.

***N,N'*-Bis(6-chlorobenzothiazol-2-yl)-*N*-methylethane-1,2-diamines (5c):** a pale-yellow solid; mp 201–204 ˚C (hexane–CH_2Cl_2); IR (KBr) 3223, 1614, 1597, 1449 cm^{-1}; ^1H NMR δ 3.20 (s, 3H), 3.82 (br s, 2H), 3.96 (t, *J* = 5.5 Hz, 2H), 6.44 (br s, 1H), 7.23 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.28 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 1H), 7.46 (d, *J* = 8.7 Hz, 1H), 7.50 (d, *J* = 2.3 Hz, 1H), 7.56 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 39.66, 43.91, 51.72, 119.48, 119.62, 120.45 (two overlapped C's), 126.35, 126.53, 126.65, 126.86, 131.80, 132.02, 151.16, 151.19, 166.59, 169.43; MS *m/z* 408 (37, M^+), 224 (100). Anal. Calcd for $C_{17}H_{14}Cl_2N_4S_2$: C, 49.88; H, 3.45; N, 13.69. Found: C, 49.80; H, 3.40; N, 13.79.

***N,N'*-Bis(6-chlorobenzothiazol-2-yl)-*N,N'*-diethylethane-1,2-diamines (5d):** A beige solid; mp 157–158 ˚C (hexane–$CHCl_3$); IR (KBr) 1597, 1541, 1442 cm^{-1}; ^1H NMR δ 1.29 (t, *J* = 7.3 Hz, 6H), 3.54 (q, *J* = 7.3 Hz, 4H), 3.87 (s, 4H), 7.24 (dd, *J* = 8.7, 2.3 Hz, 2H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.55 (d, *J* = 2.3 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 12.77, 47.68, 47.84, 119.43, 120.30, 126.10, 126.32, 131.98, 151.77, 167.35; MS *m/z* 450 (27, M^+), 252 (100). Anal. Calcd for $C_{20}H_{20}Cl_2N_4S_2$: C, 53.21; H, 4.47; N, 12.41.

Found: C, 53.14; H, 4.62; N, 12.37.

***N,N'*-Bis(6-chlorobenzothiazol-2-yl)propane-1,3-diamines (5e):** a pale-yellow solid; mp 219–220 °C (hexane–$CHCl_3$); IR (KBr: 3215, 1605, 1556, 1430 cm^{-1}; ^1H NMR δ 2.01 (quint, J = 6.0 Hz, 2H), 3.65 (br s, 4H), 6.14 (br s, 2H), 7.26 (dd, J = 8.2, 2.3 Hz, 2H), 7.46 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 2.3 Hz, 2H); ^{13}CNMR (DMSO-d_6) δ 28.26, 41.64, 118.77, 120.58, 124.56, 125.63, 131.92, 151.46, 166.67; MS m/z 408 (79, M^+), 238 (100). Anal. Calcd for $C_{17}H_{14}Cl_2N_4S_2$: C, 49.88; H, 3.45; N, 13.69. Found: C, 49.60; H, 3.43; N, 13.62.

***N,N'*-Bis(6-bromobenzothiazol-2-yl)-*N,N'*-diethylethane-1,2-diamines (5f):** a beige solid; mp 155–157 °C (hexane–$CHCl_3$); IR (KBr) 1593, 1541, 1441 cm^{-1}; ^1H NMR δ 1.29 (t, J = 7.3 Hz, 6H), 3.53 (q, J = 7.3 Hz, 4H), 3.87 (s, 4H), 7.38 (d, J = 0.9 Hz, 4H), 7.69 (t, J = 0.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.76, 47.70, 47.84, 113.26, 119.91, 123.09, 129.08, 132.48, 152.12, 167.35; MS m/z 538 (67, M^+), 283 (100). Anal. Calcd for $C_{20}H_{20}Br_2N_4S_2$: C, 44.46; H, 3.73; N, 10.37. Found: C, 44.39; H, 3.94; N, 10.10.

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