An Efficient Synthesis of Benzothiazoles by Direct Condensation of Carboxylic Acids with 2-Aminothiophenol under Microwave Irradiation

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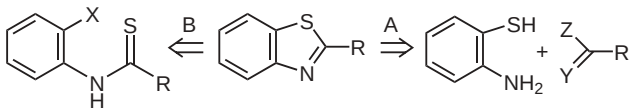
Abstract: Carboxylic acids are converted to benzothiazoles by direct condensation with 2-aminothiophenol under microwave irradiation in the absence of solvent.

Key words: benzothiazoles, carboxylic acids, 2-aminothiophenol, solvent-free, microwave

Benzothiazoles constitute an important class of compounds with profound interest to medicinal/industrial chemists as compounds bearing the benzothiazolyl moiety exhibit diverse biological properties such as antitumor,[1] antimicrobial,[2] antiglutamate/antiparkinson[3], broad spectrum Ca^{+2} channel antagonist,[4] inhibition of enzymes such as aldose reductase,[5] monoamine oxidase,[6] lipoxygenase,[7] cyclooxygenase,[8] acetylcholine esterase,[9] thrombine,[10] proteases,[11] H^+-K^+ ATPase,[12] carbonic anhydrase,[13] HCV helicase,[14] plant growth regulation,[15] and have industrial applications as antioxidants[16] and vulcanization accelerators.[17]

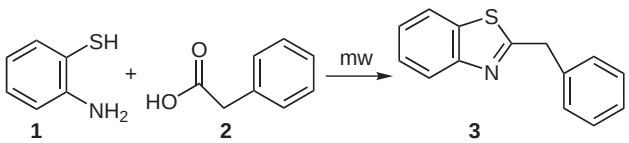
The various synthetic strategies that might be adopted for the construction of a benzothiazole moiety are depicted in Scheme 1.



Scheme 1 Strategies for the synthesis of benzothiazoles. X = H, Cl, Br, I, SMe; Y = O, Se; Z = H, OH, OR, NH_2

The methodologies developed following the strategy A involve the reaction of 2-aminothiophenol (**1**) with carboxylic acids or its derivatives. The reaction of **1** with carboxylic acids requires excess of polyphosphoric acid at 150–220 °C for 2–4 hours[14,18] or P_2O_5–$MeSO_3H$ at 70 °C for 10 hours.[19] The condensation with selenoesters[20] and selenoamides[21] is carried out in ethanol for prolonged period. Reaction with aldehydes involves silica or montmorillonite clay catalyzed oxidative cyclodehydration under microwave irradiation.[22] The synthesis adopting strategy B include the oxidative radical cyclization of thioanilides by the treatment with large excess of potassium ferricyanide at 90 °C under basic conditions,[18,23] base promoted intramolecular nucleophilic aromatic substitution of *o*-halothiobenzanilides in NMP or DMF at 150 °C for 2 hours,[24] and demethylative cylclization of *o*-(methylthio)anilides with phosphonitrile dichloride in dioxane under reflux for 8–10 hours.[25] Other approaches deal with the reaction of copper(I) thiobenzoate with 2-iodoaniline in HMPT at 110 °C for 3 hours,[26] and **1** with haloaromatics through palladium catalyzed carbonylation under high pressure in the presence of 2,6-lutidine in dimethyl acetamide[27] and with β-chlorocinnamaldehyde derivatives under microwave irradiation catalyzed by *p*-TsOH.[28] However, these methodologies suffer from one or more of the disadvantages such as the lack of ease of availability/preparation of the starting material, prolonged reaction time (14 h to 4 d), use of costly, air sensitive, and toxic substances, requirement of excess of reagents/catalysts, and harsh reaction conditions and necessitate the development of alternate synthetic route.

We reasoned that the direct condensation of a carboxylic acid with 2-aminothiophenol (strategy A) should be the ideal methodology. However, the poor leaving group property of the OH^- anion does not make the direct condensation an easy process and hence makes it essential to employ strong acids or activate the carboxylic acid by converting to various derivatives. We thought that the application of microwave irradiation should drive the reaction to achieve the required activation energy for the cyclocondensation. In order to establish the best operative condition 2-aminothiophenol (**1**) was treated with phenyl acetic acid (**2**) (Scheme 2) under various conditions (Table 1).



Scheme 2 Synthesis of benzothiazole by direct condensation of **1** with **2** under microwave irradiation

The best result was obtained by irradiation of a mixture of **1** (1 equiv) and **2** (1.5 equiv) for 20 min using full microwave power (entry 6). A decrease in the product yield was observed in using 60% power (entry 7). Use of stoichiometric amounts of the reagent mixed with silica gel did not afford any desired product (entry 2).

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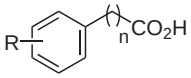
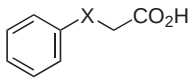
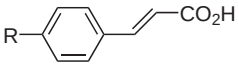
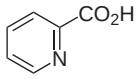
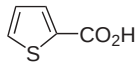
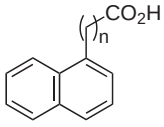
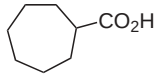
Table 1 Cyclocondensation of **1** with **2** under Microwave Irradiation[a]

Entry	**1**:**2**[b]	Power[c]	Time (min)	Yield (%)[d]
1	1:1	Full	30	51
2	1:1	Full	30	Nil[e]
3	1:2	Full	30	66
4	1:2	Full	20	81
5	1:2	Full	10	25
6	1:1.5	Full	20	95
7	1:1.5	60%	20	80

[a] The mixture of **1** and **2** was heated in a microwave oven using micro mode of operation.
[b] Molar ratio for a 2.5 mmol scale reaction of **1**.
[c] The full power is 1.35 KW.
[d] GCMS yield of 2-benzylbenzothiazole (**3**).
[e] The reaction was carried in admixture with silica gel.

In order to establish the generality of the process, various carboxylic acids were treated with **1** under microwave irradiation and the results are summarized in Table 2. Excellent results were obtained in most of the cases. Excellent chemoselectivity was observed for substrates susceptible to undergo nucleophilic substitution reactions, Michael addition, and reduction as the sulfhydryl moiety in **1** is a good nucleophile and thiols are capable of functioning as single electron transfer agents.[29] Thus no nucleophilic aromatic substitution of the chlorine atom (entries 5, 6) took place.[30] No nucleophilic substitution of the phenoxide and thiophenoxide moieties was observed during the reaction with phenoxyacetic acid and thiophenoxyacetic acid, respectively (entries 10, 11). Although thiols are commonly used for aryl methyl ether cleavage,[31] no competitive demethylation was observed for substrates containing aryl methyl ether functionality (entries 3, 4, 7, 8, 13). However, the inferior results obtained with aromatic carboxylic acids were due to the tendency of sublimation of these acids. The reactions with 1-hydroxy-2-naphthoic acid and 2-hydroxy-3-naphthoic acid did not afford any benzothiazole and the formation of 1-naphthol and 2-naphthol was observed (GCMS), respectively, as the sole product, probably arising out of decarboxylation under microwave irradiation. The reaction of thiophene-2-carboxylic acid (entry 15) led to an intractable product mixture and the expected product was obtained in 45% yield by carrying out the reaction in the presence of boric acid.[32] Cinnamic acid (entry 12) and 4-methoxycinnamic acid (entry 13) afforded the desired benzothiazole derivative without any competitive Michael addition[33] or reduction of the double bond.[34] In most of the cases the product obtained after the usual work up was of sufficient purity (GCMS) and did not require further purification.

Table 2 Cyclocondensation of Various Carboxylic Acids with **1** under Microwave Irradiation[a]

Entry	Carboxylic Acid	Yield (%)[b,c]
		
1	R = H; n = 1	90
2	R = H; n = 2	82
3	R = 4-OMe; n = 1	88
4	R = 3-OMe; n = 1	92
5	R = 2-Cl; n = 0	63
6	R = 4-Cl; n = 0	31
7	R = 2-OMe; n = 0	40
8	R = 2,3-*di*-OMe; n = 0	30
9	R = H; n = 0	12
		
10	X = O	97
11	X = S	89
		
12	R = H	32
13	R = OMe	74
14		69
15		45[d]
		
16	n = 0	67
17	n = 1	45
18		50

[a] The mixture of the carboxylic acid (1.5 equiv) and **1** (1 equiv) was irradiated under microwave using a domestic microwave oven under micro mode of operation using full power (1.35 KW) for 20 min.
[b] Isolated yield of the corresponding 2-substituted benzothiazole.
[c] All new compounds were fully characterized by IR, ^{1}H NMR, MS, and elemental analyses.
[d] The reaction was carried out in the presence of 1 equiv of boric acid.

In order to find out whether the formation of bis-benzothiazole is possible during the reaction with a dicarboxylic acid, phthalic acid and succinic acid were treated with **1** under similar conditions. The GCMS analysis of the crude product mixture obtained from the reaction of phthalic acid revealed it to be a mixture of the expected bis-benzothiazole **4**, 2-phenyl benzothiazole and some unidentified product (highest molecular ion fragment at *m/z* = 223) in a ratio of 67:10:23, respectively. The crude product on chromatographic purification afforded **4** in 45% yield. The formation of 2-phenyl benzothiazole may be explained as the result of decarboxylation of the initially formed mono-benzothiazole **5** wherein the adjacent heteroatom may assist the decarboxylation through hydrogen bond formation. Similar hydrogen bond assisted decarboxylation was observed during the reactions with 1-hydroxy-2-naphthoic acid and 2-hydroxy-3-naphthoic acid wherein 2-naphthol could be identified (GCMS) as the sole product. The crude product obtained from the reaction with succinic acid resulted in 23% yield of 1,2-*di*-(2-benzothiazolyl)ethane (**6**) after chromatographic purification (Figure 1).

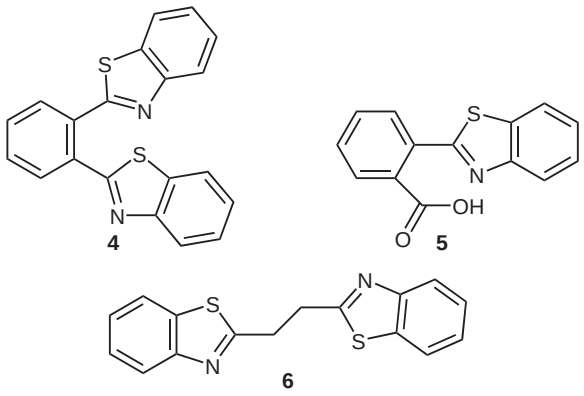


Figure 1

In conclusion, the present work describes an efficient new methodology for the synthesis of 2-substituted benzothiazoles form carboxylic acids without the involvement of any dehydrating agents.

Typical Procedure for the Synthesis of Benzothiazole: A mixture of 2-aminothiophenol (**1**; 250 mg, 2 mmol) and phenylacetic acid (**2**; 408.5 mg, 3 mmol) in a beaker (25 mL) was placed in a domestic microwave oven (BPL, Model BMC 900T, 1.35 KW, 2450 MHz) and irradiated (micromode, full power) for 20 min. The reaction mixture was allowed to reach r.t. and extracted with Et_2O (2 × 15 mL). The combined ethereal extracts were washed with sat. aq $NaHCO_3$ (2 × 10 mL), brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure to afford crude product which was purified through column chromatography in hexane:EtOAc (94:06) to give pure 2-benzylbenzothiazole[35] (**3**; 405 mg, 90%). IR (KBr): 3063, 3028, 1513, 1432 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.43 (s, 2 H), 7.20–7.46 (m, 7 H), 7.76 (d, *J* = 7.9 Hz, 1 H), 7.99 (d, *J* = 8.1 Hz, 1 H). MS (EI): *m/z* = 225 (M^+), 148 ($M^+ – C_6H_5$), 91 ($C_7H_7^+$). The remaining reactions were carried out following this general procedure and in each occasion the product was characterized by IR, NMR and MS. The physical data (mp, IR, NMR and MS) of 2-(4-chlorophenyl)benzothiazole[21] (entry 6 in Table 2), 2-phenylbenzothiazole[21,26,36] (entry 9 in Table 2), 2-(pyridyl)benzothiazole[21] (entry 14 in Table 2), 2-(thienyl)benzothiazole[21] (entry 15 in Table 2) compared well with those of the literature report. New data were generated in case of the following known compounds.

2-(Phenylethyl)benzothiazole[37] (entry 2 in Table 2): IR (KBr): 3377, 3059, 2925, 2852, 1609, 1495, 1519, 1474, 1454, 1312, 1122 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ = 3.11 (t, *J* = 7.6 Hz, 2 H), 3.39 (t, *J* = 7.6 Hz, 2 H), 6.43–6.48 (m, 1 H), 6.77 (d, *J* = 8.1 Hz, 1 H), 7.00–7.18 (m, 3 H), 7.34–7.39 (m, 1 H), 7.43–7.48 (m, 1 H), 7.91 (d, *J* = 8.0 Hz, 1 H), 7.97 (d, *J* = 7.9 Hz, 1 H). MS (EI): *m/z* = 239 (M^+), 162 ($M^+ – C_6H_5$), 148 ($M^+ – C_7H_7$), 91 ($C_7H_7^+$).

2-(2-Chlorophenyl)benzothiazole[22] (entry 5 in Table 2): IR (KBr): 3055, 2924, 2849, 1558, 1454, 1318, 1221 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.45 (m, 3 H), 7.50–7.55 (m, 2 H), 7.95 (d, *J* = 7.6 Hz, 1 H), 8.14 (d, *J* = 8.1 Hz, 1 H), 8.21 (dd, *J* = 5.7 Hz, 3.7 Hz, 1 H). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 121.36, 123.42, 125.41, 126.26, 127.07, 130.77, 131.10, 131.71, 132.20, 132.66, 136.06, 152.45, 164.12. MS (EI) *m/z* = 245 (M^+), 210 ($M^+ – Cl$).

2-(2-Methoxyphenyl)benzothiazole[38] (entry 7 in Table 2): MS (EI): *m/z* = 241 (M^+), 212 ($M^+ – OCH_3$), 136 ($M^+ – C_7H_7O$).

2-(2,3-Dimethoxyphenyl)benzothiazole[39] (entry 8 in Table 2): IR (KBr): 3055, 2919, 2849, 1642, 1591, 1504, 1318, 1167 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.98 (s, 3 H), 4.14 (s, 3 H), 7.25 (d, *J* = 6.2 Hz, 1 H), 7.40–7.46 (m, 1 H), 7.62–7.67 (m, 1 H), 7.72–7.77(m, 1 H), 7.98 (d, *J* = 7.9 Hz, 1 H), 8.88 (d, *J* = 8.4 Hz, 1 H), 8.95 (d, *J* = 8.2 Hz, 1 H). MS (EI): *m/z* = 271 (M^+), 256 ($M^+ – CH_3$), 241 ($M^+ – C_2H_6$), 224 ($M^+ – C_2H_6O$).

2-Styrylbenzothiazole[40] (entry 12 in Table 2): MS (EI): *m/z* = 237 (M^+), 236 ($M^+ – 1$), 102 ($M^+ – C_7H_5NS$).

2-(4-Methoxystyryl)benzothiazole[41] (entry 13 in Table 2): MS (EI): *m/z* = 267 (M^+), 252 ($M^+ – CH_3$), 236 ($M^+ – OCH_3$).

2-(1-Naphthyl)benzothiazole[42] (entry 16 in Table 2): IR (KBr): 3020, 1590, 1406, 1215, 759 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.44 (m, 1 H), 7.50–7.62 (m, 4 H), 7.90–7.97 (m, 4 H), 8.20 (d, *J* = 8.1 Hz, 1 H), 8.93 (d, *J* = 8.3 Hz, 1 H). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 121.38, 123.54, 124.97, 125.28, 125.88, 126.26, 126.49, 127.62, 128.39, 129.38, 130.64, 130.75, 131.06, 134.0, 135.43, 154.14, 167.61. MS (EI): *m/z* = 261 (M^+).

2-(2-Carboxyphenyl)benzothiazole (5):[43] IR (KBr): 3066, 2852, 2757, 2563, 2469, 1702, 1458, 1437, 1317, 1291, 1253, 1239, 1220, 1081 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ = 4.26 (br. s, 1 H), 7.50–7.55 (m, 2 H), 7.58–7.63 (m, 1 H), 7.67–7.75 (m, 2 H), 7.79–7.81 (m, 1 H), 7.85–7.88 (m, 1 H), 8.08 (d, *J* = 7.9 Hz, 1 H), 8.17 (d, *J* = 7.9 Hz, 1 H). ^{13}C NMR (300 MHz, DMSO): δ = 122.06, 122.84, 125.42, 126.43, 129.20, 130.35, 130.42, 131.07, 132.22, 133.05, 135.38, 153.0, 166.39, 168.79. MS (APCI): *m/z* = 255.9 ($M^+ + 1$), 238.3 ($M^+ – 17$).

The physical data of new compounds are provided below.

2-(4-Methoxybenzyl)benzothiazole (entry 3 in Table 2): mp 66 °C. IR (KBr): 3426, 3032, 2954, 2908, 2834, 1611, 1586, 1511, 1459, 1304, 1248, 1178, 1116 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3 H), 4.38 (s, 2 H), 6.89 (d, *J* = 8.2 Hz, 2 H), 7.26–7.35 (m, 3 H), 7.42–7.47 (m, 1 H), 7.79 (d, *J* = 7.8 Hz, 1 H), 7.99 (d, *J* = 8.0 Hz, 1 H). MS (EI): *m/z* = 255 (M^+), 240 ($M^+ – CH_3$), 224 ($M^+ – OCH_3$), 91 ($C_7H_7^+$), 77 ($C_6H_5^+$). Anal. Calcd for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49; S, 12.56. Found: C, 70.63; H, 5.20; N, 5.51; S, 12.62.

2-(3-Methoxybenzyl)benzothiazole (entry 4 in Table 2): IR (KBr): 3059, 2937, 1605, 1512, 1472 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.74(s, 3 H), 4.37 (s, 2 H), 6.79 (d, *J* = 8.3 Hz, 1 H), 6.90–6.94 (m, 2 H), 7.20–7.30 (m, 2 H), 7.38–7.43 (m, 1 H), 7.73

(d, J = 7.9 Hz, 1 H), 7.98 (d, J = 8.1 Hz, 1 H). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 40.46, 55.02, 113.24, 115.28, 121.92, 121.97, 123.20, 125.28, 126.41, 130.33, 136.13, 139.08, 153.67, 160.38, 171.46. MS (EI): m/z = 255 (M^+), 240 ($M^+ - CH_3$), 224 ($M^+ - OCH_3$), 91 ($C_7H_7^+$), 77 ($C_6H_5^+$). Anal. Calcd for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49; S, 12.56. Found: C, 70.61; H, 5.19; N, 5.53; S, 12.51.

2-(Phenoxymethyl)benzothiazole (entry 10 in Table 2): mp 86 °C. IR (KBr): 3052, 2902, 1593, 1523, 1492, 1436, 1255 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.50 (s, 2 H), 6.99–7.06 (m, 3 H), 7.29–7.35 (m, 2 H), 7.38–7.43 (m, 1 H), 7.48–7.53 (m, 1 H), 7.90 (d, J = 8.0 Hz, 1 H), 8.04 (d, J = 8.1 Hz, 1 H). MS (EI): m/z = 241 (M^+), 164 ($M^+ - C_6H_5$), 148 ($M^+ - C_6H_5O$), 77 ($C_6H_5^+$). Anal. Calcd for $C_{14}H_{11}NOS$: C, 69.68; H, 4.59; N, 5.80; S, 13.29. Found: C, 69.63; H, 4.62; N, 5.76; S, 13.31.

2-(Thiophenoxymethyl)benzothiazole (entry 11 in Table 2): mp 44 °C. IR (KBr): 3057, 2997, 1582, 1508, 1479, 1434, 1312, 1245, 1094, 1063 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.49 (s, 2 H), 7.13–7.34 (m, 4 H), 7.37–7.46 (m, 3 H), 7.77 (d, J = 7.8 Hz, 1 H), 7.94 (d, J = 8.2 Hz, 1 H). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 36.81, 121.65, 122.90, 125.11, 126.05, 127.01, 129.13, 129.78, 134.51, 135.69, 153.11, 169.94. MS (EI): m/z = 257 (M^+), 148 ($M^+ - C_6H_5S$), 77 ($C_6H_5^+$). Anal. Calcd for $C_{15}H_{13}NS$: C, 65.33; H, 4.31; N, 5.44; S, 24.92. Found: C, 65.42; H, 4.37; N, 5.49; S, 24.83.

2-(1-Naphthylmethyl)benzothiazole (entry 17 in Table 2): mp 103 °C. IR (KBr): 3055, 2900, 1922, 1805, 1591, 1554, 1509, 1432, 1244 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.84 (s, 2 H), 7.19–7.24 (m, 1 H), 7.37–7.51 (m, 5 H), 7.64 (d, J = 7.9 Hz, 1 H), 7.79–7.84 (m, 2 H), 8.01 (d, J = 8.1 Hz, 1 H), 8.05–8.08 (m, 1 H). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 38.36, 121.42, 122.64, 123.88, 124.66, 125.49, 125.83, 125.87, 126.48, 127.79, 128.45, 128.72, 131.79, 133.20, 133.93, 135.56, 153.09, 171.77. MS (EI): m/z = 275 (M^+). Anal. Calcd for $C_{18}H_{13}NS$: C, 78.51; H, 4.76; N, 5.09; S, 11.64. Found: C, 79.13; H, 5.03; N, 5.67; S, 11.47.

2-(1-Cycloheptyl)benzothiazole (entry 18 in Table 2): IR (KBr): 2926, 2854, 1609, 1512, 1458, 1440, 1274 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50–1.70 (m, 6 H), 1.70–2.00 (m, 4 H), 2.10–2.30 (m, 2 H), 3.20–3.35 (m, 1 H), 7.30–7.36 (m, 1 H), 7.41–7.46 (m, 1 H), 7.84 (d, J = 7.9 Hz, 1 H), 7.97 (d, J = 8.1 Hz, 1 H). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 26.51, 28.04, 35.35, 45.48, 121.51, 122.48, 124.50, 125.80, 134.62, 152.92, 178.83. MS (EI): m/z = 231 (M^+). Anal. Calcd for $C_{14}H_{17}NS$: C, 72.68; H, 7.41; N, 6.05; S, 13.86. Found: C, 72.54; H, 7.48; N, 6.11; S, 13.82.

1,2-Bis(2-Benzothiazolyl)benzene (4): mp 94 °C. IR (KBr): 3358, 3055, 2915, 1594, 1433, 1314, 1222, 1017 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.40 (m, 2 H), 7.46–7.51 (m, 2 H), 7.64 (dd, J = 5.7 Hz, 3.3 Hz, 2 H), 7.81 (d, J = 7.9 Hz, 2 H), 7.95 (dd, J = 5.7 Hz, 3.3 Hz, 2 H), 8.05 (d, J = 8.3 Hz, 2 H). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 121.52, 123.73, 125.36, 126.23, 130.31, 130.98, 133.56, 136.64, 153.21, 166.19. MS (APCI): m/z = 345.3 (M^+ +1). Anal. Calcd for $C_{20}H_{12}N_2S_2$: C, 69.74; H, 3.51; N, 8.13; S, 18.62. Found: C, 69.78; H, 3.54; N, 8.10; S, 18.58.

1,2-Bis(2-benzothiazolyl)ethane (6): mp 137 °C. IR (KBr): 3055, 2310, 1904, 1782, 1591, 1510, 1454, 1440, 1319, 1212, 1090, 1061 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.73 (s, 4 H), 7.32–7.37 (m, 2 H), 7.43–7.48 (m, 2 H), 7.81 (d, J = 7.9 Hz, 2 H), 7.99 (d, J = 8.1 Hz, 2 H). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 33.21, 121.54, 122.71, 124.94, 126.03, 135.19, 153.12, 169.18. MS (APCI) m/z = 297.0 (M^+ +1). Anal. Calcd for $C_{16}H_{12}N_2S_2$: C, 64.83; H, 4.08; N, 9.45; S, 21.64. Found: C, 64.86; H, 4.10; N, 9.41; S, 21.63.

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