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A convenient synthesis of 2-mercapto and 2-chlorobenzothiazoles is described. The key feature of the synthesis is an exclusive *ortho*-selective nucleophilic aromatic substitution reaction of *ortho*-haloanilines with potassium/sodium *O*-ethyl dithiocarbonate under mild conditions. Subsequent intra-molecular cyclization affords 2-mercaptobenzothiazoles in high yields. The 2-mercaptobenzothiazoles are readily converted to corresponding 2-chlorobenzothiazoles upon treatment with sulfuryl chloride.

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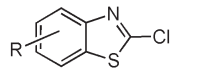
Benzothiazole-containing compounds are common synthetic targets in drug discovery due to their interesting biological and pharmacological properties [1-7]. Despite numerous synthetic methods available for benzothiazoles, facile and scaleable routes to highly versatile benzothiazole building blocks, such as 2-chlorobenzothiazoles (Figure 1), are still lacking [8-15]. We have previously reported that di- and polyhaloanilines bearing an *ortho* halogen atom undergo efficient nucleophilic aromatic substitution reactions with anionic sulfur nucleophiles, exclusively at the *ortho* position [16]. Specifically, with *O*-ethyl dithiocarbonate anion as the nucleophile, sequential addition and cyclization lead to the formation of halogenated 2-mercaptobenzothiazoles in excellent yields (Scheme 1).



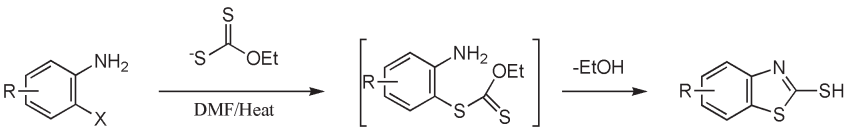
R = halide, alkyl, NO_2

Figure 1

In this paper, we report the application of this discovery in the synthesis of a variety of 2-mercapto and 2-chlorobenzothiazoles from commercially available *ortho*-haloanilines.

The results from this study are summarized in Table 1. A variety of substituted 2-mercaptobenzothiazoles (**1a-10a**) were prepared following a standard protocol [16]. When the reaction was performed on 2,3- or 2,4-dihaloanilines, the desired 6/7-halo-2-mercapto benzothiazoles were obtained in near quantitative yields (Table 1, entries 1-4). As expected by the basic rules for nucleophilic aromatic substitution reactions [17], the *ortho* halogen and substitution of the 2-haloaniline had a strong influence on the reaction rate: The reactions with o*rtho*-chloroanilines were slower than with o*rtho*-fluoroanilines (Table 1, entries 4 and 5) while electron-withdrawing substitutions increased the reaction rate (Table 1, entries 5-6). In this study, a large excess amount of potassium *O*-ethyl dithiocarbonate was typically necessary to ensure complete reaction of the *ortho*-haloaniline. However, an activated substrate such as 5-nitro-2-fluoroaniline, quickly converted to 2-mercaptobenzothiazole with only 1.2 equivalent of the *O*-ethyl dithiocarbonate nucleophile (Table 1, entry 6). The same reaction afforded 2-mercapto-5-(trifluoromethyl)[1,3]thiazolo[5,4-*b*]pyridine in a modest yield (Table 1, entry 7). This method was also effective in preparing an alkyl 2-mercaptobenzothiazole (Table 1, entry 8). Remarkably, in the cases where *ortho*-haloanilines were deactivated by the strong electron-donating groups OH and NH_2, the reaction occurred smoothly with sodium *O*-ethyl dithiocarbonate to afford the desired 2-mecaptobenzothiazole products in 75 % and 83 % isolated yields, respectively (Table 1, entries 9-10). Notably, both reactions were complete in a short period of time based on ^{1}H NMR analysis.

Scheme 1



X = F, Cl, Br
R = mono-halide or halide combinations

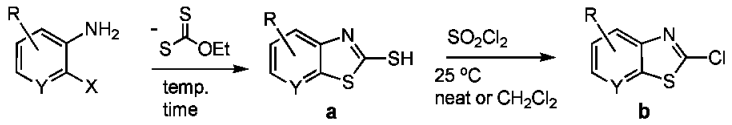
From the corresponding 2-mercaptobenzothiazoles, synthetically versatile 2-chlorobenzothiazoles (**1b-9b**) were readily prepared following a literature procedure [18]. The reaction was carried out in neat sulfuryl chloride at room temperature. An equal volume of CH_2Cl_2 was added to improve mixing when necessary. In most cases, the desired chlorinated products were formed in

less than 2 hours, and isolated without chromatography in satisfactory yields (Table 1, entries 1-8). 2-Mercaptobenzothiazole **9a** was treated under the same conditions to afford 2,7-di-Cl-6-OH-benzothiazole as the major product (Table 1, entry 9). 5-Amino-2-mercaptobenzothiazole **10a** failed to react due to its insolubility in SO_2Cl_2/CH_2Cl_2 (Table 1, entry 10).

In conclusion, we have demonstrated a versatile synthesis of various 2-mercaptobenzothiazoles *via* a selective nucleophilic aromatic substitution with *ortho*-haloanilines in good yields. A number of novel 2-chlorobenzothiazoles were also prepared from the corresponding 2-mercaptobenzothiazoles.

Table 1

Synthesis of 2-Chloro-benzothiazoles *via* 2-Mercaptobenzothiazoles



entry	R	X	Y	Temp.(°C)	Time	%yield(**a**) [a]	% yield(**b**) [a]
1	4-F	F	CH	95	4 h	99(**1a**)	99(**1b**)
2	3-F	F	CH	120	2 h	96(**2a**)	59(**2b**)
3	4-Br	F	CH	90	3 h	98(**3a**)	99(**3b**)
4	3-Cl	C	CH	120	18 h	88(**4a**)	53(**4b**)
5	4-CF_3	Cl	CH	120	10 h	92(**5a**)	91(**5b**)
6 [b]	5-NO_2	F	CH	100	2 h	95(**6a**)	99(**6b**)
7	6-CF_3	Cl	N	125	20 h	65(**7a**)	75(**7b**)
8	4-iPr	Br	CH	100	24 h	92(**8a**)	93(**8b**)
9 [c]	4-OH	F	CH	90	4 h	75(**9a**)	40(**9b**) [d]
10 [c]	5-NH_2	F	CH	120	4 h	83(**10a**)	NR [e]

[a] Isolated yields. [b] 1.2 Equiv. of KSC(=S)OEt was used. [c] NaSC(=S)OEt was used. [d] Isolated product was 2,7-di-Cl-6-OH-1,3-benzothiazole. [e] Compound **10a** was insoluble in SO_2Cl_2/CH_2Cl_2.

EXPERIMENTAL

Typical Procedure for 2-Mercaptobenzothiazole Formation.

A solution of 2,4-difluoroaniline (15.0 g, 116.2 mmol, 1.0 eq), potassium *O*-ethyl dithiocarbonate (41.0 g, 255.6 mmol, 2.2 eq) in 75 mL anhydrous DMF was heated at 95 °C for 4 hours under nitrogen. NMR analysis of a reaction aliquot showed no starting material remaining. The reaction mixture was cooled to room temperature, and diluted with H_2O (150 mL) and 1 *N* HCl solution (200 mL) to induce precipitation. Stirring was continued for 30 minutes. The solid precipitate was collected by filtration, and rinsed with water. The wet filter cake was dissolved in 250 mL EtOAc, and dried over Na_2SO_4. EtOAc was removed by rotary evaporation, and the residue was dried *in vacuo* to afford 6-fluoro-2-mercaptobenzothiazole (**1a**) (19.5 g, 91%); ^{1}H NMR (DMSO-d_6): δ 13.80 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.28 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 189.98, 159.41, 138.48, 131.28, 115.38, 114.06, 109.60; ESI-LCMS *m/z* (MH^+) 186.

Anal. Calcd. for $C_7H_4FNS_2$: C, 45.39; H, 2.18; N, 7.56. Found: C, 45.40; H, 2.25, N, 7.54.

Typical Procedure for 2-Chlorobenzothiazole Formation.

To 6-fluoro-2-mercaptobenzothiazole (19.3 g, 104.2 mmol) cooled in an ice-water bath, was added 50 mL SO_2Cl_2 at below room temperature under nitrogen, and the suspension was stirred at room temperature for 2 hours. NMR analysis showed no starting material remaining. The reaction mixture was poured onto ice water with stirring. Precipitation was formed, and stirring was continued for 2 hours. The solid precipitate was collected by filtration, and rinsed with water. The solid was dried *in vacuo* to afford 2-chloro-6-fluoro-benzothiazole (**1b**) (19.5 g, 99%); ^{1}H NMR (DMSO-d_6): δ 8.00 (m, 2H), 7.40 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 160.20, 152.92, 147.66, 137.40, 124.44, 116.15, 109.68; EI-GCMS *m/z* (M^+) 187.

Anal. Calcd. for C_7H_3ClFNS: C, 44.81; H, 1.61; N, 7.47. Found: C, 44.56; H, 1.40, N, 7.29.

7-Fluoro-2-mercaptobenzothiazole (**2a**).

This compound has the following properties: ^{1}H NMR (DMSO-d_6): δ 14.00 (s, 1H), 7.40 (m, 1H), 7.12 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 188.24, 154.71, 152.29, 142.81, 142.74, 128.49, 128.41, 115.27, 115.04, 109.71, 109.53, 108.45, 108.41; ESI-LCMS *m/z* (MH^+)186.

Anal. Calcd. for $C_7H_4FNS_2$: C, 45.39; H, 2.18; N, 7.56. Found: C, 45.10; H, 1.95, N, 7.47.

2-Chloro-7-fluoro-benzothiazole (**2b**).

This compound has the following properties: ^{1}H NMR (DMSO-d_6): δ 7.83 (dd, *J* = 8.2, 0.90 Hz,1H), 7.59 (dt, *J* = 8.2, 5.7 Hz, 1H), 7.44 (ddd, *J* = 9.9, 8.3, 1.1 Hz, 1H). EI-GCMS m/z (M^+) 187.

6-Bromo-2-mercaptobenzothiazole (**3a**).

This compound has the following properties: ^{1}H NMR (DMSO-d_6): δ 13.82 (s, 1H), 7.95 (d, J = 1.9 Hz, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.19 (d, J = 8.6 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 190.34, 140.99, 131.96, 130.75, 124.73, 116.91, 114.50. ESI-LCMS m/z (MH^+) 248.

Anal. Calcd. for $C_7H_4BrNS_2$: C, 34.16; H, 1.64; N, 5.69. Found: C, 34.08; H, 1.61; N, 5.60.

2-Chloro-6-bromo-benzothiazole (**3b**).

This compound has the following properties: ^{1}H NMR (DMSO-d_6): δ 8.38 (d, J = 1.7 Hz, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.65 (d, J = 8.6 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 154.28, 149.82, 138.04, 130.73, 125.57, 124.56, 119.32. EI-GCMS m/z (M^+) 249.

Anal. Calcd. for $C_7H_3BrClNS$: C, 33.83; H, 1.22; N, 5.64. Found: C, 33.69; H, 1.10; N, 5.44.

7-Chloro-2-mercaptobenzothiazole (**4a**).

This compound has the following properties: ^{1}H NMR (DMSO-d_6): δ 7.35 (m, 2H), 7.20 (dd, J = 7.8, 1.1 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 188.66, 141.95, 128.61, 127.95, 124.51, 123.42, 111.07. ESI-LCMS m/z (MH^+) 202.

Anal. Calcd. for $C_7H_4ClNS_2$: C, 41.69; H, 2.00; N, 6.94. Found: C, 41.56; H, 1.94, N, 6.81.

2,7-Dichloro-benzothiazole (**4b**).

This compound has the following properties: ^{1}H NMR (DMSO-d_6): δ 7.97 (dd, J = 7.8, 1.3 Hz, 1H), 7.62 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 152.01, 150.13, 134.54, 127.86, 125.19, 124.41, 120.82. ESI-LCMS m/z (MH^+) 204.

Anal. Calcd. for $C_7H_3Cl_2NS$: C, 41.20; H, 1.48; N, 6.86. Found: C, 40.98; H, 1.24, N, 6.91.

6-Trifluoromethyl-2-mercaptobenzothiazole (**5a**).

This compound has the following properties: ^{1}H NMR (DMSO-d_6): δ 14.00 (b, 1H), 8.18 (s, 1H), 7.72(d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 191.76, 144.51, 130.67, 125.02, 124.90, 124.77, 120.10, 113.42. EI-GCMS m/z (M^+) 235.

Anal. Calcd. for $C_8H_4F_3NS_2$: C, 40.84; H, 1.71; N, 5.95. Found: C, 41.06; H, 1.58, N, 5.82.

2-Chloro-6-trifluoromethyl-benzothiazole (**5b**).

This compound has the following properties: ^{1}H NMR ($CDCl_3$): δ 8.09 (s, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.73 (d, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 156.30, 152.91, 136.24, 128.05, 124.00, 123.93, 123.46, 119.02; EI-GCMS m/z (M^+) 237.

Anal. Calcd. for $C_8H_3ClF_3NS$: C, 40.43; H, 1.27; N, 5.89. Found: C, 40.71; H, 1.27, N, 5.83.

5-Nitro-2-mercaptobenzothiazole (**6a**).

This compound has the following properties: ^{1}H NMR (DMSO-d_6): δ 8.12 (d, J = 8.0 Hz, 1H), 7.90 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 197.80, 152.08, 147.29, 124.87, 128.54, 124.59, 112.69. EI-GCMS m/z (M^+) 213.

Anal. Calcd. for $C_7H_4N_2O_2S_2$: C, 39.61; H, 1.90; N, 13.20. Found: C, 40.01; H, 1.82, N, 13.07.

2-Chloro-5-nitro-benzothiazole (**6b**).

This compound has the following properties: ^{1}H NMR (DMSO-d_6): δ 8.75 (s, 1H), 8.39 (d, J = 8.9 Hz, 1H), 8.33 (d, J = 9.0 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 157.83, 150.69, 147.42, 143.34, 124.62, 120.95, 118.16. EI-GCMS m/z (M^+) 214.

Anal. Calcd. for $C_7H_3ClN_2O_2S$: C, 39.17; H, 1.41; N, 13.05. Found: C, 39.12; H, 1.65, N, 12.78.

5-(Trifluoromethyl)[1,3]thiazolo[5,4-*b*]pyridine-2-thiol (**7a**).

This compound has the following properties: ^{1}H NMR (DMSO-d_6): δ 14.00 (b, 1H), 8.18 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 191.76, 144.51, 130.67, 125.02, 124.90, 124.77, 120.10, 113.42. EI-GCMS m/z (M^+) 235.

Anal. Calcd. for $C_8H_4F_3NS_2$: C, 40.84; H, 1.71; N, 5.95. Found: C, 41.06; H, 1.58, N, 5.82.

2-Chloro-5-(trifluoromethyl)[1,3]thiazolo[5,4-*b*]pyridine (**7b**).

This compound has the following properties: ^{1}H NMR (DMSO-d_6): δ 8.66 (d, J = 8.5 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H); ^{13}C NMR (DMSO-d_6): _ 161.76, 160.96, 150.36, 147.77, 135.98, 125.43, 123.84; ESI-LCMS m/z (MH^+) 239.

Anal. Calcd. for $C_7H_2ClF_3N_2S$: C, 35.23; H, 0.84; N, 11.74. Found: C, 35.65; H, 0.75, N, 11.51.

6-Isopropyl-2-mercaptobenzothiazole (**8a**).

This compound has the following properties: ^{1}H NMR (DMSO-d_6): δ 13.80 (s, 1H), 7.65 (s, 1H), 7.26 (d, J = 8.4 Hz, 1H), 7.20 (d, J = 8.0Hz, 1H), 2.92 (m, 1H), 1.20 (d, J = 6.7 Hz, 6H); ^{13}C NMR (DMSO-d_6): δ 189.44, 145.50, 139.78, 129.85, 126.24, 119.62, 113.00, 34.45, 25.12; ESI-LCMS m/z (MH^+) 210.

Anal. Calcd. for $C_{10}H_{11}NS_2$: C, 57.38; H, 5.30; N, 6.69. Found: C, 57.32; H, 5.22; N, 6.68.

2-Chloro-6-isopropyl-benzothiazole (**8b**).

This compound has the following properties: ^{1}H NMR (DMSO-d_6): δ 7.96 (s, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.43 (d, J = 8.4Hz, 1H), 3.04 (m, 1H), 1.25 (d, J = 6.8 Hz, 6H); ^{13}C NMR (DMSO-d_6): δ 152.04, 149.13, 147.17, 136.35, 126.61, 122.69, 119.96, 34.81, 25.25; ESI-LCMS m/z (MH^+) 212.

Anal. Calcd. for $C_{10}H_{10}ClNS$: C, 56.73; H, 4.76; N, 6.62. Found: C, 56.51; H, 4.55; N, 6.41.

6-Hydroxyl-2-mercaptobenzothiazole (**9a**).

This compound has the following properties: ^{1}H NMR (DMSO-d_6): δ 13.48 (s, 1H), 9.68 (s, 1H), 7.10 (d, J = 8.4 Hz, 1H), 7.03 (d, J = 2.5 Hz, 1H), 6.80 (dd, J = 8.7, 2.5 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 187.93, 155.13, 134.67, 131.36, 115.71, 113.60, 108.18; ESI-LCMS m/z (MH^+) 184.

Anal. Calcd. for $C_7H_5NOS_2$: C, 45.88; H, 2.75; N, 7.64. Found: C, 45.49; H, 2.52; N, 7.32.

2,7-Di-chloro-6-hydroxy-benzothiazole (**9b**).

This compound has the following properties: ^{1}H NMR (DMSO-d_6): δ 10.87 (s, 1H), 7.76 (d, J = 8.7 Hz, 1H), 7.19 (d, J = 8.7 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 151.98, 148.36, 143.34, 136.97, 121.92, 116.87, 110.14. ESI-LCMS m/z (MH^+) 220.

Anal. Calcd. for $C_7H_3Cl_2NOS$: C, 38.20; H, 1.37; N, 6.36. Found: C, 38.03; H, 1.52; N, 6.15.

5-Amino-2-mercaptobenzothiazole (**10a**).

This compound has the following properties: ^{1}H NMR (DMSO-d_6): δ 13.31 (b, 1H), 7.22 (d, J = 9.0 Hz, 1H), 6.53 (m,

2H), 5.46 (b, 2H); ^{13}C NMR (DMSO-d_6): δ 189.70, 149.16, 142.86, 122.28, 115.40, 112.67, 97.34. ESI-LCMS *m/z* (MH^+) 183.

Anal. Calcd. for $C_7H_6N_2S_2$: C, 46.13; H, 3.32; N, 15.37. Found: C, 46.50; H, 3.14, N, 14.99.

RERENCES AND NOTES

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