Facile Synthesis of 2-(Substitutedbenzylsulfanyl)-benzothiazoles and their Antimicrobial Activity Screening

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A simple and convenient procedure for the preparation of 2-(substitutedbenzylsulfanyl)benzothiazoles by the reaction of 2-mercaptobenzothiazole and benzyl bromides in acetone/K_2CO_3 has been reported and the compounds have been screened for their potential antimicrobial activities.

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Introduction.

Benzothiazoles have been shown to exhibit a wide variety of biological activities. Many compounds containing this heterocyclic nucleus are of either industrial [1] or biological [2] importance. Similarly, benzothiazole-2-thiol and its derivatives have also been reported to have potent biological activities, such as antimicobacterial activity [3], cyclooxygenase inhibitors [4] *etc*. We were interested in the synthesis of 2-(substituted-benzylsulfanyl)benzothiazoles in connection with our work on benzothiazole compounds of probable biological importance.

Results and Discussion.

A perusal of literature revealed that these compounds can be prepared by the reaction of 2-mercaptobenzothiazole with benzyl halides in the presence of a strong base like sodium in ethanol [5,3]. Although the use of strong bases such as NaOH gives good yields of the S-benzylated products, but the disadvantage lies with the formation of competing side products such as benzyl ethers [6]. Recently an alternative approach has been reported for the synthesis of title compounds under CsF-Celite [7] conditions. Other approaches include the use of dibenzylcarbonate [8] in the presence of catalytic amounts of DABCO or DBU for the benzylation. However, the availability of substituted dibenzyl carbonates limits this method. Use of Phase Transfer Catalysis (PTC) conditions in the presence of strong base like NaOH [4,9] have also been employed to synthesise the title compound although in less yields 32 % & 15%, respectively.

It is evident from the literature that though there are some methods available for the preparation of these title compounds, yet there is no simple and efficient method for the synthesis of these important heterocyclics without the use of either expensive reagents, strong bases or PTC conditions. In this paper, we wish to report a simple but efficient methodology for the synthesis of 2-(substitutedbenzylsulfanyl)benzothiazoles in excellent yields (Figure 1).

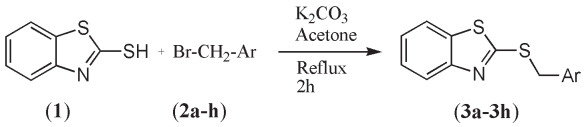
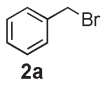
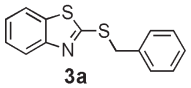
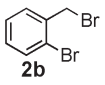
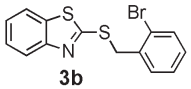
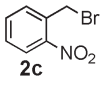
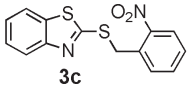
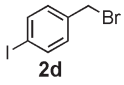
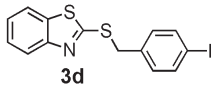
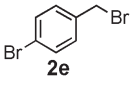
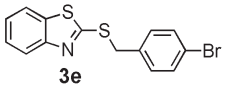
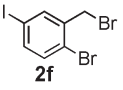
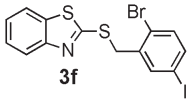
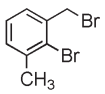
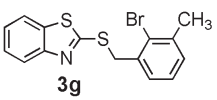
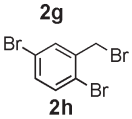
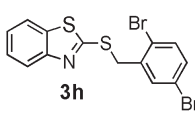


Figure 1

Reaction of 2-mercaptobenzothiazole, **1** with benzyl bromide (**2a**, Ar=Ph) in refluxing acetone in the presence of anhydrous potassium carbonate as base for 2 hr, gave the corresponding 2-benzylsulfanylbenzothiazole (**3a**, Ar-=Ph) in 98 % yield. The product was identified with the spectral

Table 1

2-(Substitutedbenzylsulfanyl)benzothiazoles Prepared from 2-Mercaptobenzothiazole

Sr. No.	Benzyl Bromide	Product	Yield (%) [a]
1	 **2a**	 **3a**	98
2	 **2b**	 **3b**	96
3	 **2c**	 **3c**	95
4	 **2d**	 **3d**	97
5	 **2e**	 **3e**	94
6	 **2f**	 **3f**	95
7	 **2g**	 **3g**	98
8	 **2h**	 **3h**	96

[a] Yields refer to the Isolated yields.

Table 2

Growth Inhibition Activity [a] of 2-Substituted-benzylsulfanylbenzothiazoles **3a-3h** Against *B. subtilis, E. coli, M. luteus, P. aeruginosa,C. albicans* and *A. niger in vitro*

Compd.	*B. subtilis*		*E. coli*		*M. Luteus*		*P. aeruginosa*		*C. albicans*		*A. niger*	
	AM1	AM11	AM1	AM11	AM1	AM11	AM1	AM11	AM1	AM11	AM1	AM11
3a	- -	- -	6.8	6.6	- -	- -	- -	- -	- -	6.2	6.9	6.0
3b	- -	- -	- -	- -	- -	- -	- -	- -	7.1	6.0	- -	- -
3c	- -	- -	- -	- -	- -	- -	- -	- -	6.3	- -	- -	- -
3d	- -	- -	6.9	- -	- -	- -	- -	- -	6.7	7.0	- -	8.2
3e	- -	- -	- -	6.4	- -	- -	- -	- -	- -	6.1	- -	- -
3f	- -	- -	6.9	7.2	- -	- -	- -	- -	- -	6.9		
3g	- -	- -	- -	- -	- -	- -	- -	- -	7.0	6.3	- -	- -
3h	- -	- -	7.6	6.2	- -	- -	- -	- -	8.0	6.7	- -	6.0

[a] Diameter (in mm) of inhibition zones; AM1: Antibiotic medium N°1 (pH=6.5); AM11: Antibiotic medium N°11 (pH=7.9).

data and by comparison with the authentic sample [5]. Similary, compound **1** was reacted with other substituted benzyl bromides (**2b-2h**) under similar conditions to get the corresponding 2-(substituted-benzylsulfanyl)-benzothiazoles (**3b-3h**) in almost quantitative yields (Table 1). All the new products were characterized by ^{1}H-, ^{13}C-NMR, mass spectra and elemental analysis data. All the compounds synthesized herein were screened for their potential antimicrobial activities using disk diffusion method. The results are measured as the diameters of inhibition zones for each micro-organism and the details are presented in Table 2. Since, 2-(substituted-benzylsulfanyl)-benzothiazoles constitute an important class of heterocyclics found in bioactive compounds, the methodology described here may find useful applications in the synthesis of drug intermediates and other bioactive compounds containing this heterocyclic moiety.

Conclusion.

In conclusion, we have reported a convenient and useful methodology for the synthesis of 2-(substituted-benzylsulfanyl)-benzothiazoles in excellent yields. The advantage of this methodology is the use of very mild reaction conditions, which can tolerate various functional groups that can be used for further synthetic manipulations. Further, commercial availability of large number of benzyl bromides or easy methods of their preparation makes this reaction a more attractive choice. All the compounds were tested for antimicrobial screening. However, only few compounds exhibited moderate activity against *E. coli*, *C. albicans* and *A. niger* in a preliminary screening.

EXPERIMENTAL

Melting points are uncorrected and were recorded on a MRVIS Series, Lab India Instrument. TLC analysis was done using precoated silica gel plates and visualization was done using Iodine/UV lamp. IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer. ^{1}H and ^{13}C-NMR spectra were recorded in $CDCl_3$ on a Bruker 400 MHz spectrometer using TMS as internal standard. Mass spectra were recorded on a Hewlett Packard Model No- 5989A mass spectrometer operating at 70 eV. Elemental analysis was carried out on a Perkin–Elmer Series –II CHN Analyzer 2400. The starting material, 2-mercaptobenzothiazole has been obtained from commercial suppliers.

General Procedure.

A mixture of 2-mercaptobenzothiazole **1** (2 mmole), respective benzyl bromide (**2a-2h**, 2 mmol), finely grounded anhydrous K_2CO_3 (4 mmol) in acetone was refluxed for 2 hr (TLC monitoring). The reaction mixture was then cooled to room temperature and filtered. Evaporation of the filtrate yielded the crude products (**3a-3h**). The crude products were purified by recrystallisation using a mixture of hexane-ethyl acetate.

Physical and Spectral Data of Compounds

2-Benzylsulfanylbenzothiazole (**3a**).

This compound was obtained as white crystals (hexane-ethyl acetate), mp 38-40 °C (Lit [5] 39-40); ir (potassium bromide): 3092, 3045, 2920, 1495, 1454, 1309, 1240, 1124, 1070, 1019, 998 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 4.62 (s, 2H), 7.24-7.34 (m, 4H), 7.40-7.46 (m, 3H), 7.81(d, *J*= 8.0Hz, 1H), 7.90 (d, *J*= 8.0Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 37.73, 121.00, 121.57, 124.29, 126.06, 127.76, 128.70, 129.13, 135.35, 136.19, 153.17, 166.40; ms: m/z(%I) 259 (M^++2, 10.9), 258 (M^++1, 16.6), 257 (M^+, 100), 225 (7.6), 224 (41.9), 166 (8.4), 122 (4), 108 (5.7), 92 (5.8), 91 (73.4), 69 (7.4), 65 (9.8).

Anal. Calcd. for $C_{14}H_{11}NS_2$: C, 65.33; H, 4.31; N, 5.44. Found: C, 65.26; H, 4.28; N, 5.31.

2-(2-Bromo-benzylsulfanyl)-benzothiazole (**3b**).

This compound was obtained as pale yellow prisms (hexane-ethyl acetate), mp 40-41 °C; ir (potassium bromide): 3060, 1558, 1456, 1427, 1309, 1264, 1026, 994 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 4.73 (s, 2H), 7.12 (t, *J*= 7.6Hz, 1H), 7.21-7.30(m, 2H), 7.42 (t, *J*= 7.6Hz, 1H), 7.58 (dd, *J*= 11.6 & 8.0Hz, 2H), 7.73(t, *J*= 8.0Hz, 1H), 7.90(d, *J*= 8.0Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 37.89, 121.02, 121.56, 124.30, 124.81, 126.03, 127.63, 129.36, 131.33, 133.02, 135.48, 136.09, 153.09, 166.01; ms: m/z(%I) 337 (M^++2, 55.9), 336 (M^++1, 9.5), 335 (M^+, 53), 258 (10.8), 257 (18.8), 256 (100), 249 (16), 223 (42.5), 181 (6.3), 171

(71.3), 169 (79.3), 166 (16), 135 (8.6), 122 (8.5), 108 (13), 90 (31.5), 89 (25), 69 (17), 63 (11), 59 (11), 43 (12.6).

Anal. Calcd. for $C_{14}H_{10}BrNS_2$: C, 50.00; H, 3.00; N, 4.17. Found: C, 50.23; H, 3.16; N, 4. 24.

2-(2-Nitro-benzylsulfanyl)-benzothiazole (**3c**).

This compound was obtained as off-white solid (hexane-ethyl acetate), mp 64-66 °C; ir (potassium bromide): 3059, 2875, 1522, 1457, 1425, 1357, 1309, 1019, 782 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.95 (s, 2H), 7.28 (t, *J*= 7.6Hz, 1H), 7.38-7.44(m, 2H), 7.53 (t, *J*= 7.6Hz, 1H), 7.71 (d, *J*= 8.0Hz, 1H), 7.81(d, *J*= 8.0Hz, 1H), 7.90(d, *J*= 8.4Hz, 1H), 8.04(d, *J*= 8.4Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 34.20, 121.05, 121.57, 124.40, 125.24, 126.08, 128.72, 132.75, 133.34, 133.52, 135.53, 148.37, 152.84, 165.73; ms: m/z(%I) 304 (M^++2, 4.3), 303 (M^++1, 5.8), 302 (M^+, 31.5), 284 (3.7), 256 (12), 254(11), 252 (7), 237 (10), 223 (7.2), 169 (13.7), 168 (14.2), 167 (100), 166 (17.3), 136 (19), 122 (8.3), 108 (17.3), 105 (6.4), 89 (12), 86 (47.6), 84 (88), 78 (35.3), 77 (10), 69 (10.6), 65 (10.5), 63 (7.7), 49 (12), 47 (6.7).

Anal. Calcd. for $C_{14}H_{10}N_2O_2S_2$: C, 55.61; H, 3.33; N, 9.26. Found: C, 55.71; H, 3.11; N, 9.01.

2-(4-Iodo-benzylsulfanyl)-benzothiazole (**3d**).

This compound was obtained as pale yellow solid (hexane-ethyl acetate), mp 60-62 °C; ir (potassium bromide): 3044, 2921, 1582, 1482, 1455, 1426, 1309, 1076, 1006, 826 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.53 (s, 2H), 7.20 (d, *J*= 8.0Hz, 2H), 7.30(t, *J*= 7.6Hz, 1H), 7.42 (t, *J*= 7.6Hz, 1H), 7.64(d, *J*= 8.0Hz, 2H), 7.74(d, *J*= 8.0Hz, 1H), 7.89(d, *J*= 8.0Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 37.06, 93.28, 121.06, 121.57, 124.48, 126.18, 130.83, 131.05, 131.82, 135.33, 136.19, 137.80, 152.94, 165.89; ms: m/z(%I) 385 (M^++2, 10.9), 384 (M^++1, 17.8), 383 (M^+, 100), 350 (20.6), 337 (4), 297 (4.8), 231 (4), 224 (6), 223 (27.5), 218 (6), 217 (67.2), 181 (3.6), 169 (8.6), 166 (5.7), 149 (3.5), 131(5.8), 108 (4.6), 90 (13.5), 89 (10.9), 63 (3.3).

Anal. Calcd. for $C_{14}H_{10}INS_2$: C, 43.87; H, 2.63; N, 3.65. Found: C, 43.64; H, 2.74; N, 3.67.

2-(4-Bromo-benzylsulfanyl)-benzothiazole (**3e**).

This compound was obtained as off-white solid (hexane-ethyl acetate), mp 68-70 °C; ir (potassium bromide): 3075, 2967, 1913, 1582, 1455, 1426, 1309, 1071, 1019, 828 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.55 (s, 2H), 7.28-7.40 (m, 3H), 7.41-7.45 (m, 3H), 7.74 (d, *J*= 8.0, 1H), 7.89 (d, *J*= 8.0Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 36.96, 94.88, 121.06, 121.59, 121.73, 124.46, 126.16, 130.83, 131.82, 135.54, 152.99, 165.85; ms: m/z(%I) 337 (M^++2, 100), 336 (M^++1, 17.2), 335 (M^+, 89.5), 320 (3.4), 304 (24), 303 (5), 302 (21.2), 223 (41.5), 181 (4), 171 (57.7), 169 (64), 166 (8), 122 (6.4), 108 (7.8), 90 (16), 89 (9), 69 (4.2).

Anal. Calcd. for $C_{14}H_{10}BrNS_2$: C, 50.00; H, 3.00; N, 4.17. Found: C, 50.12; H, 2.96; N, 4.19.

2-(2-Bromo-5-Iodo-benzylsulfanyl)-benzothiazole (**3f**).

This compound was obtained as a pale yellow crystals (hexane-ethyl acetate), mp 79-81 °C; ir (potassium bromide): 2952, 1883, 1566, 1505, 1459, 1420, 1366, 1074, 1020, 981 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.64 (s, 2H), 7.25-7.32 (m, 2H), 7.42 (dd, *J*= 8.0 & 2.0Hz, 2H), 7.29-7.52 (m, 1H), 7.92(d, *J*= 8.0Hz, 1H), 8.0(d, *J*= 2.0Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 37.15, 92.35, 121.04, 121.62, 124.40, 124.63, 126.12, 134.47, 135.48, 138.20, 138.42, 140.32, 152.99, 165.36; ms: m/z(%I) 463 (M^++2, 12.5), 461 (M^++1, 10), 384 (M^+, 10.7), 383 (16), 382 (100), 349 (16), 336 (4), 298 (18), 297 (15.7), 296 (19.8), 295 (13.9), 255 (10), 171 (4), 170 (6.7), 169 (9.4), 168 (7), 166 (5.7), 108 (4.4), 90 (4.2), 89 (8.7), 86 (8.9), 84 (12.9), 63 (3.6).

Anal. Calcd. for $C_{14}H_9BrINS_2$: C, 36.38; H, 1.96; N, 3.03. Found: C, 36.02; H, 1.98; N, 2.98.

2-(2-Bromo-3-methyl-benzylsulfanyl)-benzothiazole (**3g**).

This compound was obtained as a white crystalline solid (hexane-ethyl acetate), mp 77-79 °C; ir (potassium bromide): 3059, 2982, 1574, 1460, 1428, 1375, 1310, 1241, 1076, 992 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.43 (s, 3H), 4.78 (s, 2H), 7.12 (t, *J*= 7.2Hz, 2H), 7.28 (t, *J*= 8.0Hz, 1H), 7.41(t, *J*= 7.8Hz, 2H), 7.72(d, *J*= 8.0Hz, 1H), 7.90(t, *J*= 6.8Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 23.84, 38.86, 121.00, 121.54, 124.27, 126.03, 127.04, 127.39, 128.76, 130.28, 135.45, 136.40, 139.09, 153.09, 166.33; ms: m/z(%I) 351 (M^++2, 89), 350 (M^++1, 14.5), 349 (M^+, 80.9), 318 (4.9), 281 (3.5), 272 (12.8), 271 (20.8), 270 (100), 238 (14.5), 237 (65.2), 219 (4), 186 (5), 185 (49.7), 184 (6), 183 (57.8), 181 (7), 166 (10.5), 135 (4.5), 122 (4), 108 (7), 104 (14.9), 103 (12.2), 102 (3.6), 78 (4.8), 77 (5.8).

Anal. Calcd. for $C_{15}H_{12}BrNS_2$: C, 51.43; H, 3.45; N, 4.00. Found: C, 51.12; H, 3.18; N, 3.89.

2-(2, 5-Dibromo-benzylsulfanyl)-benzothiazole (**3h**).

This compound was obtained as off-white solid (hexane-ethyl acetate), mp 76-77 °C; ir (potassium bromide): 3061, 2963, 1552, 1456, 1428, 1264, 1086, 1026, 998 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.68 (s, 2H), 7.25-7.27 (m, 1H), 7.30 (t, *J*= 7.6Hz, 1H), 7.44 (t, *J*= 7.2Hz, 2H), 7.75 (d, *J*= 8.0Hz, 1H), 7.82 (d, *J*= 2.4Hz, 1H), 7.92 (d, *J*= 8.0Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 37.33, 121.07, 121.28, 121.61, 123.43, 124.47, 126.18, 132.32, 134.27, 134.37, 135.45, 138.30, 152.90, 165.47; ms: m/z(%I) 415 (M^++2, 23.4), 413 (M^+, 11), 355 (M^+, 9.3), 338 (11.2), 337 (18.5), 336 (100), 335 (18.5), 334 (95.6), 303 (26), 301 (7.4), 268 (13.2), 266 (13.2), 255 (12.7), 251 (16.6), 249 (35.6), 247 (14.8), 223 (4.2), 185 (4), 170 (9.5), 168 (10.4), 149 (6.5), 108 (5.2), 89 (4.2).

Anal. Calcd. for $C_{14}H_9Br_2NS_2$: C, 40.50; H, 2.19; N, 3.37. Found: C, 40.48; H, 2.38; N, 3.40.

Antimicrobial Activity of Compounds **3a-3h**.

Test disks (6 mm in diameter) impregnated with 100 μg of the appropriate sample were used to test both antibacterial and antifungal activities at pH 6.5 and 7.9 respectively. Disks were applied on the surface of plates containing each 25 ml of Antibiotic medium N°1 (pH=6.5) or N°11(pH=7.9), inoculated with 10^6 CFU/ml of the microorganisms. The following strains were used to test the activities: *Bacillus subtilis* ATCC 6633 CCM-A-10, *Escherichia coli* ATCC 11105 CCM-A-424, *Micrococcus luteus* ATCC 9341 CCM-A-45, *Pseudomonas aeruginosa* ATCC 9027 CCM-A-39, *Candida albicans* ATCC 10231 and *Aspergillus niger* ATCC 16404. Growth inhibition was tested after a 24 hour incubation at 37 °C. All the results are expressed as the diameter (in mm) of inhibition zones, and are shown in Table 2.

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