Facile Synthesis and Antimicrobial Properties of 2-(Substituted-benzylsulfanyl)-1*H*-benzimidazoles

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A simple and convenient procedure for the preparation of 2-benzylthiobenzimidazoles by the reaction of 2-mercaptobenzimidazole and benzyl bromides in acetone/potassium carbonate condition has been reported and the compounds were screened for their potential antimicrobial activities.

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Benzimidazoles have been shown to exhibit a large number of biological activities. The biological activities of the compounds containing this basic moiety have been well documented [1]. Some of them like thiabendazole, mebendazole and albendazole are widely used as anti-helmintic drugs [2]. Similarly, benzimidazole-2-thiol and its derivatives have also been reported to have potent biological activities, such as proton pump inhibitors [3] antiulcer activity [4], inhibitors of H^+/K^+ ATP ase [5].

We were interested in the synthesis of 2-benzylthiobenzimidazoles in connection with our work on drug intermediates containing benzimidazole moiety. In this regard, literature survey revealed that these compounds can be prepared by the reaction of 2-mercaptobenzimidazole with alkyl or aryl halides in the presence of bases such as NaH/DMF (8%) [6], K_2CO_3/EtOH (20%) [5], DMF/K_2CO_3 [3b] (35 %), in low yields. In some instances, the formation of both the S and N benzyl derivatives have been reported even by the use of aq. Na_2CO_3 in isopropyl alcohol [7]. Using strong bases such as NaOH/EtOH [8] gave good yield of the S-arylated products, however the disadvantage lies with the formation of competing side products such as benzyl ethers and N-alkylated products.

To overcome this problem recently the use of a phase-transfer catalysis (PTC) has also been reported in the presence of strong bases like NaOH [9] and KOH [10]. This indicates that though there are several methods available in the literature for the synthesis of these title compounds, there is no simple and convenient method available for the synthesis of these important heterocyclics without the use of either strongly basic conditions or PTC.

In this communication, we wish to report a simple but efficient method for the synthesis of 2-benzylthiobenzimidazoles in excellent yields (Figure 1).

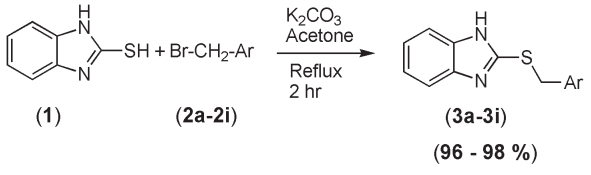


Figure 1

In a typical procedure equimolar amounts of 2-mercaptobenzimidazole and benzyl bromide (**2a**, Ar=Ph) are refluxed in acetone in the presence of anhydrous potassium carbonate as base for 2 hr, giving the corresponding 2-benzylthiobenzimidazole (**3a**, Ar-=Ph) in 98 % yield. The product was identified with spectral data and by comparision with the authentic sample [7]. Similary, 2-mercaptobenzimidazole was reacted with other substituted benzyl bromides (**2b-2i**) under similar conditions to give the corresponding 2-benzylthiobenzimidazoles (**3b-3i**) in excellent yields (Table 1). All the products were characterized by IR, ^{1}H, and ^{13}C- NMR spectral and analytical data. Since, 2-benzylthiobenzimidazoles 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.

Conclusion.

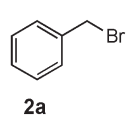
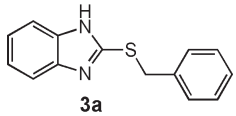
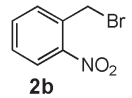
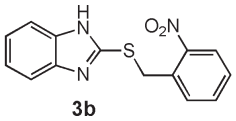
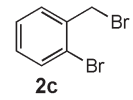
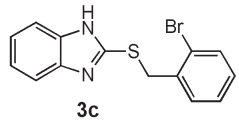
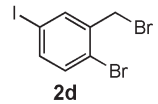
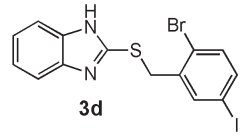
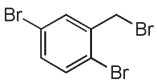
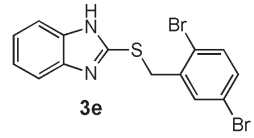
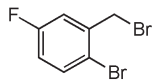
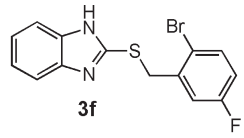
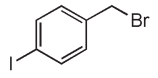
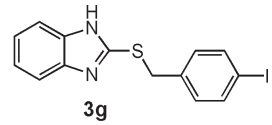
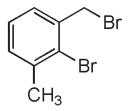
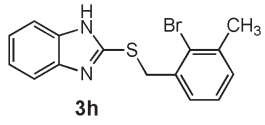
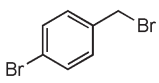
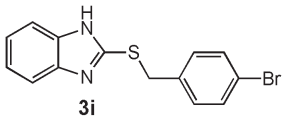
In conclusion, we have reported for the first time a convenient and useful method for the synthesis of 2-benzylthiobenzimidazoles in excellent yields. The advantage of this methodology is the use of very mild reaction conditions, which can tolerate various functional groups that can be used for further 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 activity. Only a few compounds exhibited moderate activity against *B. subtilis*, *E. coli*, *P. aeruginosa*, *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

Table 1

List of Various 2-Benzylthiobenzimidazoles Prepared

Sr. No.	Benzyl Bromide	Product	Yield (%)	M.P. (°C)
1	 **2a**	 **3a**	98	189-190 (Lit[7]. 184-85)
2	 **2b**	 **3b**	96	134 –135 (Lit[11]. 132-135)
3	 **2c**	 **3c**	97	195-198
4	 **2d**	 **3d**	97	153-155
5	 **2e**	 **3e**	98	160-161
6	 **2f**	 **3f**	96	129-130
7	 **2g**	 **3g**	96	204-205
8	 **2h**	 **3h**	98	175-176
9	 **2i**	 **3i**	97	206-207 (Lit[11]. 198-201)

Series –II CHN Analyzer 2400. The starting material, 2-mercaptobenzimidazole has been obtained from commercial suppliers.

General Procedure.

A mixture of 2-mercaptobenzimidazole **1** (2 mmole), respective benzyl bromide (**2a-2i**, 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-3i**). The crude products were purified by recrystallization using a mixture of hexane-ethyl acetate.

Spectral Properties of Compounds.

2-Benzylsulfanyl-1*H*-benzimidazole (**3a**).

IR (KBr): 3069, 2963, 2811, 1619, 1513, 1496, 1402, 1351, 1268, 1152, 1071, 1011, 980 cm^{-1}. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6/TMS): δ 4.50 (s, 2H), 7.18-7.48 (m, 9H). ^{13}C NMR (100

Table 2

Growth inhibition activity [a] of 2-substituted-benzylsulfanylbenzimidazoles **3a-3i** 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	—	—	7.0	6.1	—	—	—	—	—	6.2	6.6	6.0
3b	—	—	—	—	—	—	6.4	—		—	—	
3c	—	—	—	—	—	—	—	—	6.3	—	—	—
3d	6.3	6.8	6.0	—	—	—	—	—	6.7	7.0	—	7.1
3e	—	—	—	6.4	—	—	7.0	6.2-	—	6.1	—	—
3f	—	6.5	6.3	6.0	—	—	—	—	—	6.9	6.0	6.3
3g	—	—	—	—	—	—	6.9	—	7.0	—	—	—
3h	7.0	6.1	6.6	6.0	—	—	—	—	6.6	6.0	—	6.0
3i	—	—	—	—	—	—	—	—	—	6.1	6.4	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).

MHz): 37.17, 122.35, 127.73, 128.76, 129.04, 129.30, 129.53, 130.50, 136.81, 150.12. EI-MS (m/z, %I): 242 (M^++2, 6.4), 241 (M^++1, 18), 240 (M^+, 100), 239 (7.8), 225 (4), 208 (9.8), 207 (58), 206 (8), 163 (5.5), 149 (14), 122 (15), 92 (6.3), 91 (69), 90 (4.3), 65 (12.7), 63 (5).

2-(2-Nitrobenzylsulfanyl)-1*H*-benzimidazole(**3b**).

IR (KBr): 2790, 1607, 1573, 1534, 1399, 1350, 1271, 1151, 1014, 987 cm^{-1}. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6/TMS): δ 4.77 (s, 2H), 6.98-7.01 (m, 2H), 7.23 (t, *J* = 7.6Hz, 1H), 7.31-7.35 (m, 3H), 7.62 (d, *J*= 7.6 Hz, 1H), 7.85 (d, *J*= 8.4Hz, 1H). ^{13}C-NMR (100 MHz): 33.68, 114.09, 122.01, 125.12, 128.68, 132.70, 133.69, 133.78, 141.63, 147.97, 149.32. EI-MS (m/z, %I): 286 (M^++1, 7.55), 285 (M^+, 41.7), 240 (6), 239 (31), 237 (8), 225 (4.8), 220 (7.7), 207 (6), 206 (9), 180 (4), 151(13), 150 (100), 149 (20), 136 (21), 122 (23), 105 (4.8), 91 (6), 90 (6), 78 (20), 63 (4), 51 (4).

Anal. Calcd. for $C_{14}H_{11}N_3O_2S$: C, 58.93; H, 3.89; N, 14.73. Found: C, 59.01; H, 3.79; N, 14.81.

2-(2-Bromobenzylsulfanyl)-1*H*-benzimidazole (**3c**).

IR (KBr): 2736, 1632, 1509, 1402, 1268, 1228, 1044, 1027, 987 cm^{-1}. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6/TMS): δ 4.69 (s, 2H), 7.08-7.20 (m, 4H), 7.43 (s, 3H), 7.49-7.55 (m, 1H). ^{13}C-NMR (100 MHz): 36.99, 114.28, 121.66, 124.48, 127.65, 129.16, 131.21, 132.79, 136.79, 149.49. EI-MS (m/z, %I): 318 (M^+, 4.5), 240 (16), 239 (100), 219 (3), 207 (9.6), 206 (55), 181(6.6), 180 (7), 171 (35), 169 (49), 149 (15), 131 (11), 122 (22), 119 (7.4), 90 (32), 89(17), 69 (9.6).

Anal. Calcd. for $C_{14}H_{11}BrN_2S$: C, 52.68; H, 3.47; N, 8.78. Found: C, 52.36; H, 3.49; N, 8.80.

2-(2-Bromo-5-iodobenzylsulfanyl)-1*H*-benzimidazole(**3d**).

IR (KBr): 3070, 1620, 1513, 1457, 1400, 1348, 1274, 1195, 1154, 1076, 1022, 978 cm^{-1}. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6/TMS): δ 4.38 (s, 2H), 6.92 (dd, *J*= 6.0 & 3.2 Hz, 2H), 7.03 (d, *J*= 8.4Hz, 1H), 7.18 (dd, *J*= 8.4 & 2.4Hz, 1H), 7.24 (d, *J*= 5.6Hz, 2H), 7.68 (d, *J*= 2.4Hz, 1H). ^{13}C-NMR (100 MHz): 36.24, 92.40, 121.85, 124.36, 134.36, 138.00, 139.14, 139.92, 141.64, 149.12. EI-MS (m/z, %I): 446 (M^++2, 33), 444 (M^+, 43.8), 366 (19), 365 (100), 332 (13.8), 317 (3), 297 (12), 295 (12), 239 (11), 238 (41), 237 (15), 205 (7), 170 (11), 168 (12.8), 150 (6.1), 149 (9), 122(15), 90 (5), 89 (17), 63 (6).

Anal. Calcd. for $C_{14}H_{10}BrIN_2S$: C, 37.78; H, 2.26; N, 6.29. Found: C, 37.70; H, 2.19; N, 6.20.

2-(2,5-Dibromobenzylsulfanyl)-1*H*-benzimidazole (**3e**).

IR (KBr): 3065, 2960, 2804, 1577, 1457, 1403, 1352, 1274, 1228, 1198, 1082, 1023, 978 cm^{-1}. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6/TMS): δ 4.46 (s, 2H), 6.98 (s, 2H), 7.04 (d, *J*= 8.8Hz, 1H), 7.23 (d, *J*= 8.4Hz, 2H), 7.56 (s, 2H). ^{13}C-NMR (100 MHz): 35.98, 110.05, 117.43, 120.78, 122.79, 131.65, 133.62, 133.72, 138.75, 141.26, 148.79. EI-MS (m/z, %I): 400 (M^++4, 9), 398 (M^++2, 15.6), 396 (M^+, 7.8), 333 (5), 321 (6.5), 320 (17.4), 319 (100), 318 (22), 317 (96), 316 (4), 286 (16.5), 284 (17.8), 251 (11.2), 249 (22), 247 (11), 238 (8), 237 (7), 205 (5), 170 (7), 168 (7.5), 163(6), 150 (9.3), 149 (17.6), 122 (23), 90 (5.6), 89 (12.6), 63 (5.5).

Anal. Calcd. for $C_{14}H_{10}Br_2N_2S$: C, 42.24; H, 2.53; N, 7.04. Found: C, 41.98; H, 2.58; N, 7.22.

2-(2-Bromo-5-fluorobenzylsulfanyl)-1*H*-benzimidazole(**3f**).

IR (KBr): 3046, 2957, 2790, 1604, 1581, 1562, 1469, 1400, 1349, 1271, 1234, 1157, 1031, 1012, 984 cm^{-1}. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6/TMS): δ 4.48 (s, 2H), 6.62-6.67 (m, 1H), 6.97 (dd, *J*= 6.0 & 3.2Hz, 2H), 7.17 (dd, *J*= 9.2 & 3.2Hz, 1H), 7.28-7.32 (m, 3H). ^{13}C-NMR (100 MHz): 36.57, 36.59, 116.21, 116.43, 118.17, 118.35, 118.59, 118.62, 122.02, 133.88, 133.96, 139.01, 139.09, 149.13, 160.37, 162.84. EI-MS (m/z, %I): 338 (M^++2, 11), 336 (M^+, 10.8), 259 (6.6), 258 (17.5), 257 (100), 256 (6.6), 225 (6.9), 224 (26), 198 (5.6), 189 (13), 187 (12.6), 163 (4), 149 (13), 122 (17.5), 108 (13.5), 107 (11.5), 90 (4), 60 (3.5).

Anal. Calcd. for $C_{14}H_{10}BrFN_2S$: C, 49.86; H, 2.99; N, 8.31. Found: C, 50.02; H, 3.23; N, 8.02.

2-(4-Iodobenzylsulfanyl)-1*H*-benzimidazole (**3g**).

IR (KBr): 2957, 2790, 1604, 1482, 1402, 1351, 1272, 1058, 1000, 980 cm^{-1}. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6/TMS): δ 4.55 (s, 2H), 7.16-7.20 (m, 3H), 7.38 (s, 1H), 7.51 (dd, *J*= 6.0 & 3.2Hz, 2H), 7.60 (d, *J*= 8.4Hz, 2H). ^{13}C-NMR (100 MHz): 36.20, 93.08, 114.05, 122.18, 125.86, 130.76, 131.00, 136.93, 137.65, 141.60, 149.41. EI-MS (m/z, %I): 368 (M^++2, 6.6), 367 (M^++1, 16.55), 366 (100), 333 (11.5), 217 (45), 206 (13.5), 149 (6.3), 122 (7.8), 90 (13.7), 89 (8.3), 63 (3.9).

Anal. Calcd. for $C_{14}H_{11}IN_2S$: C, 45.91; H, 3.03; N, 7.65. Found: C, 45.96; H, 3.21; N, 7.62.

2-(2-Bromo-3-methylbenzylsulfanyl)-1*H*-benzimidazole (**3h**).

IR (KBr): 2804, 1588, 1506, 1437, 1395, 1361, 1271, 1226, 1025, 984 cm^{-1}. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6/TMS): δ 2.42 (s, 3H), 4.80 (s, 2H), 7.10 (m, 2H), 7.19 (dd, *J*= 6.0 & 3.2Hz, 2H), 7.39 (d, *J*= 5.6Hz, 1H), 7.54 (s, 2H). ^{13}C-NMR (100 MHz):23.82, 38.32, 122.32, 125.35, 127.14, 128.76, 130.20, 131.76, 136.64, 136.98, 138.87, 149.73. EI-MS (m/z, %I): 334 (M^++2, 22.5), 332 (M^+, 20.8), 255 (5.6), 254 (18.3), 253 (100), 221 (5.6), 220 (24.8), 185 (17.33), 183 (17), 149 (5.4), 122 (6.5), 104 (9.7), 103 (7.5), 78 (5.7), 77 (5.7).

Anal. Calcd. For $C_{15}H_{13}BrN_2S$: C, 54.06; H, 3.93; N, 8.41. Found: C, 53.91; H, 3.98; N, 8.18.

2-(4-Bromobenzylsulfanyl)-1*H*-benzimidazole (**3i**).

IR (KBr):2952, 1620, 1513, 1487, 1270, 1229, 1069, 983 cm^{-1}. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6/TMS): δ 4.52 (s, 2H), 7.16 (m, 1H), 7.29 (d, *J*= 8.8Hz, 2H), 7.35 (s, 2H), 7.40 (d, *J*= 8.4Hz, 2H), 7.65 (d, *J*= 8.0Hz, 1H). ^{13}C-NMR (100 MHz):35.99, 110.38, 117.93, 121.34, 121.53, 122.07, 130.73, 131.64, 136.52, 144.00, 149.54. EI-MS (m/z, %I): 321 (M^++3, 14), 320 (M^++2, 92.6), 319 (M^++1, 14.6), 318 (M^+, 86), 287 (14), 285 (16), 239 (3), 206 (31), 171 (100), 169 (98), 149 (64.4), 122 (65), 105 (3), 91 (14.8), 90 (73), 89 (46), 78 (7), 63 (33), 51 (7).

Anal. Calcd. For $C_{14}H_{11}BrN_2S$: C, 52.68; H, 3.47; N, 8.78. Found: C, 52.96; H, 3.62; N, 8.62.

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

All the compounds synthesized herein were screened for their potential antimicrobial activities using the disk diffusion method. Test compounds were dissolved in *N*,*N*-dimethylformamide (DMF) (Control). Test discs (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. All the experiments were carried out in duplicates. 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. From the activity studies it can be inferred that compounds containing the halogens on the phenyl ring at 2-position showed good to moderate activity against both the bacteria and fungal stains tested. For example compound **3d** having both chloro and iodo substituents showed promising activity both against bacteria and fungus. Further presence of methyl group along with bromo as in **3h** also showed good activity. However compound with a nitro substituent as in **3b** did not show much activity except against the fungal stain *P. aeruginosa.*

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