N-methylthiomethylation of benzimidazoles with DMSO and their chemoselective oxidation to sulfoxides with $NaBiO_3$

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Abstract

A straightforward one-step method for the N-methylthiomethylation of benzimidazoles has been developed employing DMSO as a solvent and as a reagent. This methodology has been applied for the synthesis of diverse N-methylthiomethyl derivatives of benzimidazoles. The products can be chemoselectively oxidized to the corresponding sulfoxides with $NaBiO_3$ in acetic acid. Both the N-methylthiomethyl derivatives of benzimidazoles and their corresponding sulfoxides are important medicinal scaffolds.

Keywords: *N*-Methylthiomethylation of benzimidazoles, oxidation, sulfoxides, DMSO, $NaBiO_3$

Introduction

The imidazole nucleus is a privileged structural sub–unit encountered in numerous biologically important molecules ranging from natural products to pharmaceuticals.[1] Several imidazole derivatives are widely used as organocatalysts,[2] ionic liquids[3] and N–heterocyclic carbenes.[4] Consequently, it is no wonder that the development of strategies for their synthesis and functionalization has instigated a growing interest in academia and in industry thereby continuing to be a significant subject in organic synthesis and medicinal chemistry.[1]

Both Burdon *et al.*[5a] and Pfitzner *et al.*[5b] found almost simultaneously that phenols can be *ortho*-methylthiomethylated by dimethylsulfoxide (DMSO) in the presence of dicyclohexylcarbodiimide (DCC) and a proton source. Later, Hayashi and Oda found that the same reaction occurred using acetic anhydride instead of DCC at room temperature.[5c] Gassman and Amick achieved the *ortho*-methylthiomethylation of phenols by the reaction of phenol and dimethylsulfide in presence of *N*-chlorosuccinimide (NCS) and triethylamine.[6a] Foote *et al.*

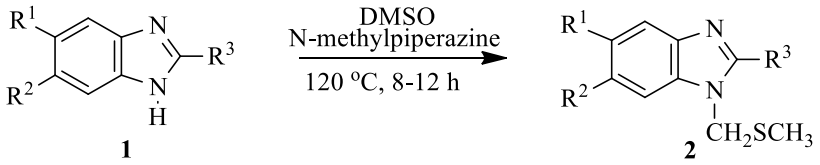
reported the *ortho*-methylthiomethylation of anilines by the reaction of anilines and dimethylsulfide in presence of *tert*-butyl hypochlorite and sodium methoxide.[6b]

As several *N*-methylthiomethyl derivatives of imidazoles are endowed with useful anti-inflammatory, analgesic and antipyretic properties,[7] we were very keen to develop similar type of reaction with imidazoles. The previous methods[7,8] for the synthesis of *N*-methylthiomethyl imidazoles include a two step method: first, the formation of trialkylsilyl derivatives of imidazoles followed by reaction with DMSO at elevated temperature. This method has some serious drawbacks like two–step reaction procedure, drastic reaction condition and complex reaction methodology. Moreover, these procedures have not been generalized to different types of benzimidazole derivatives. We therefore wanted to develop a methodology that overcomes the earlier drawbacks.

The ever-growing interest and application of sulfoxides has attracted a growing interest to develop new methodologies for sulfoxide synthesis. Organic sulfoxides are valuable intermediates for the synthesis of fine chemicals and biologically active compounds.[9]

Results and Discussions

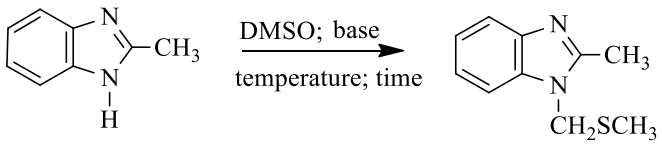
Considering the growing interest both in the conversion of imidazoles to *N*-methylthiomethyl imidazoles and in chemoselective oxidation of sulfides to sulfoxides, we, herein for the first time, report a straightforward conversion of several benzimidazoles to their N-methylthiomethyl counterparts followed by a mild, novel protocol for the chemoselective oxidation of sulfide to sulfoxide derivatives.



Scheme 1. N-Methylthiomethylation of benzimidazoles.

Initially, the reaction between 2-methylbenzimidazole and DMSO was selected as a model reaction to investigate the best reaction condition. After extensive studies with several bases, it was found that using *N*-methylpiperazine as a base at a moderate temperature produced the best yield of product after eight hours (Table 1, entry 8). The complete optimization table is given below.

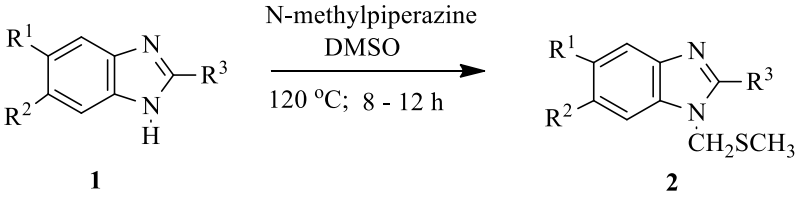
Table 1. Optimization for the N-methylthiomethylation of 2-methylbenzimidazole



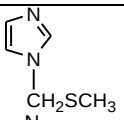
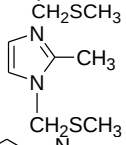
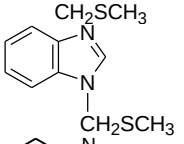
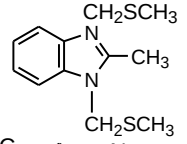
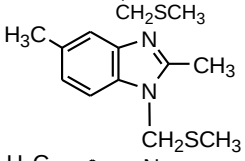
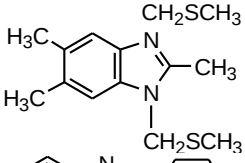
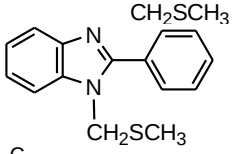
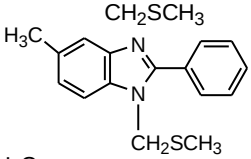
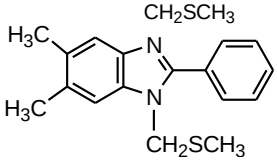
Entry	Base (equv.)	Temperature (°C)	Time (h)	Yields (%) (isolated)
1	□	160	24	20
2	Et_3N (2)	90	24	25
3	K_2CO_3 (2)	160	24	35
4	Cs_2CO_3 (2)	160	24	35
5	DABCO (2)	160	24	40
6	NaH (2)	160	24	25
7	Piperidine (2)	110	24	40
8	NMP (2)	120	8	65
9	NMP (3)	120	8	65
10	NMP (1.5)	120	8	50
11	NMP (2)	120	12	65
12	NMP (2)	160	12	65

Having established the optimized reaction conditions, imidazole and a wide variety of 2-substituted benzimidazoles were investigated (Table 2) under the same reaction conditions. As a result, a broad spectrum of N-methylthiomethylbenzimidazole(s) was obtained as shown in Table 2.

Table 2. N-Methylthiomethylation of benzimidazoles



1 **2**

Entry	Product Nos.	Products	Time (h)	Yields (%) (isolated)	References
1	**2a**		8	65	8
2	**2b**		10	59	8
3	**2c**		10	62	8
4	**2d**		8	60	8
5	**2e**		8	62	–
6	**2f**		8	66	–
7	**2g**		8.5	60	–
8	**2h**		8.5	60	–
9	**2i**		8	65	–

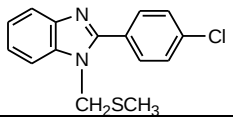
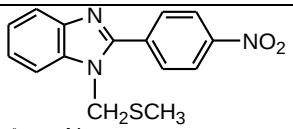
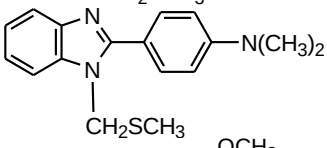
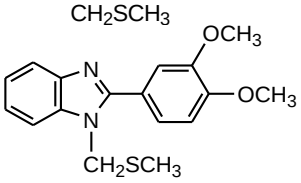
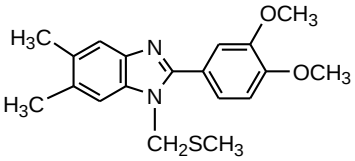
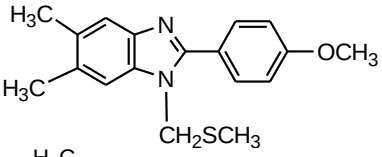
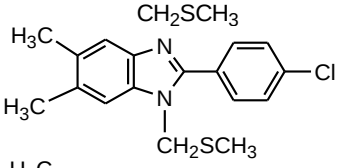
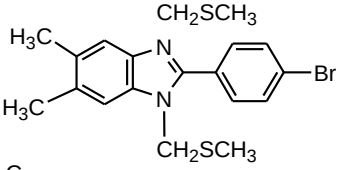
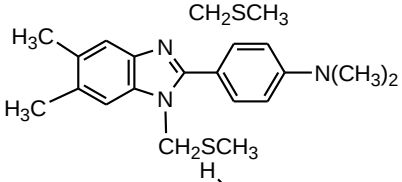
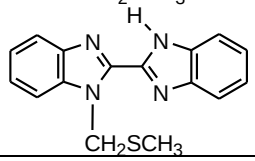
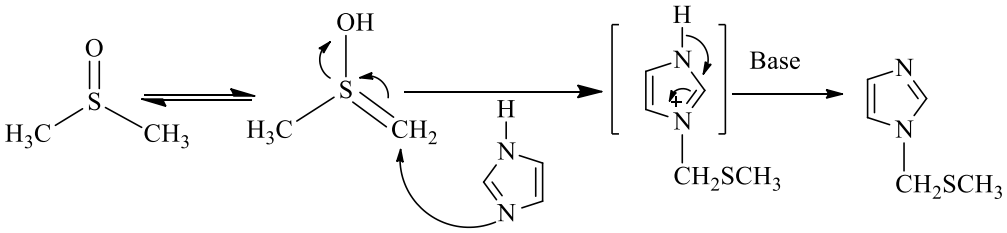
10	**2j**		10	65	–

Table 2. Continued

Entry	Product Nos.	Products	Time (h)	Yields (%) (isolated)	References
11	**2k**		12	58	–
12	**2l**		8	64	–
13	**2m**		12	58	–
14	**2n**		11	58	–
15	**2o**		10	60	–
16	**2p**		8	65	–
17	**2q**		8	65	–
18	**2r**		8	63	–
19	**2s**		12	30	–

A base catalysed mechanism for the N-methylthiomethylation of imidazole has been suggested below in which the valency of sulfur reduced from 4 (in DMSO) to 2 in the product.



Scheme 2. Probable mechanism for the base catalysed N-methylthiomethylation of imidazole.

As illustrative example, the structure of N-methylthiomethylation product of 2-phenyl benzimidazole (Table 2, entry 7) was assessed by X-ray crystallography and is given below in Figure 1.

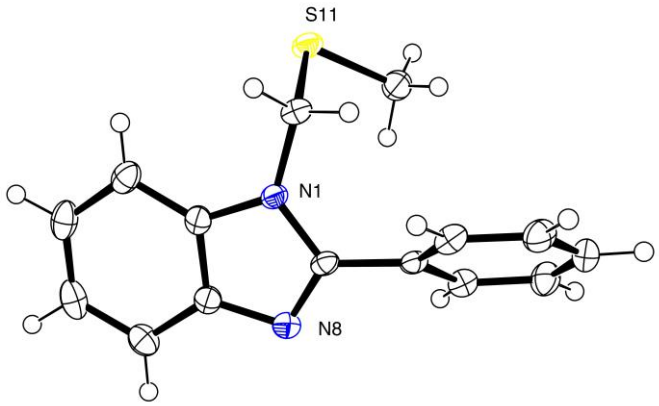
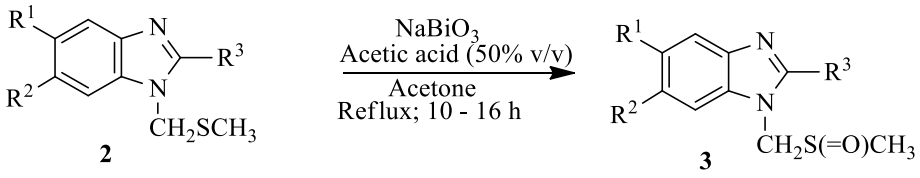


Figure 1. ORTEP diagram of product 2g in (Table 2, entry 7) with ellipsoids at 50 % probability (CCDC 780651).

The straightforward method for the synthesis of sulfoxides is the chemoselective oxidation of corresponding sulfide to sulfoxide. Therefore, once the N-methylthiomethylation of benzimidazoles is achieved, further chemoselective oxidation of these sulfides to sulfoxides came into our mind immediately. There are a lot of reagents available for the oxidation of dialkyl, alkylaryl and diaryl sulfides to sulfoxides.[10] Most of them cause over oxidation to sulfones. Therefore, the condition of the reaction, that is time, temperature and relative amounts of oxidants have to be controlled to avoid side product formation.

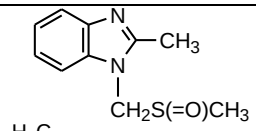
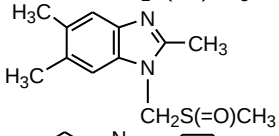
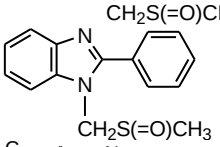
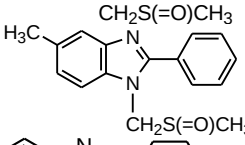
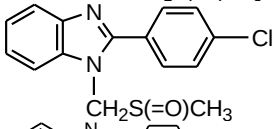
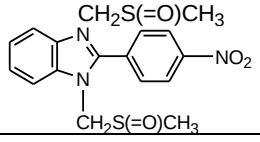
Recently, the oxidation of sulfides to sulfoxides by H_2O_2 has proved to be one of the most attractive methods.[11] Very recently, Rostami and Akradi[12] reported boric acid as a highly efficient and eco-friendly catalyst for the selective oxidation of sulfide to sulfoxide at room temperature under solvent–free condition using 30% H_2O_2 as an oxidant. We thought to test the

oxidation of our sulfides under the same reaction condition. But unfortunately, 24 h of stirring at room temperature with 1.2 equivalent of H_2O_2 (30%), 0.1 mmol of boric acid using 1 mmol of our sulfide (Table 3, entry 1) only 5% of sulfide was transformed into the desired product. Even after 24 h of heating under reflux condition using the same proportion of H_2O_2, boric acid and sulfide, only 40% transformation of the sulfide to the desired sulfoxides has been achieved. This unsatisfactory result forced us to search for a better oxidizing agent for the chemoselective oxidation of our sulfides to sulfoxides. After a thorough screening with the common oxidizing agents, $NaBiO_3$ in acetic acid came out as the best choice for chemoselective oxidation of our sulfides to sulfoxides (Scheme 3). The presence of acetic acid is extremely important as the reaction failed to produce the desired product in its absence. It has also noticed that small amounts of acetone as co–solvent increases the yield of the reaction.[13] Using this methodology a completely new class of organic sulfoxides has been prepared (Scheme 3, Table 3)



Scheme 3. Chemoselective oxidation of sulfides to sulfoxides.

Table 3. Chemoselective oxidation of sulfides to sulfoxides by $NaBiO_3$ in acetic acid

Entry	Product Nos.	Products	Time (h)	Yields (%) (isolated)
1	**3a**		12	82
2	**3b**		12	80
3	**3c**		10	80
4	**3d**		10	82
5	**3e**		14	78
6	**3f**		16	70

The mechanism of the oxidation reaction by $NaBiO_3$ in acetic acid is not clear. Kon and McNeils predicted[14] that the oxidation of phenol in acetic acid medium by $NaBiO_3$ involved a two electron oxidation and considering this reference we may predict that the oxidation of sulfides to sulfoxides in our case may also proceed through 2-electron oxidation.

The final structure of the sulfoxide was confirmed by the X-ray crystal structure of the sulfoxide product **3c** (Table 3, entry 3) which is given below in Figure 2.

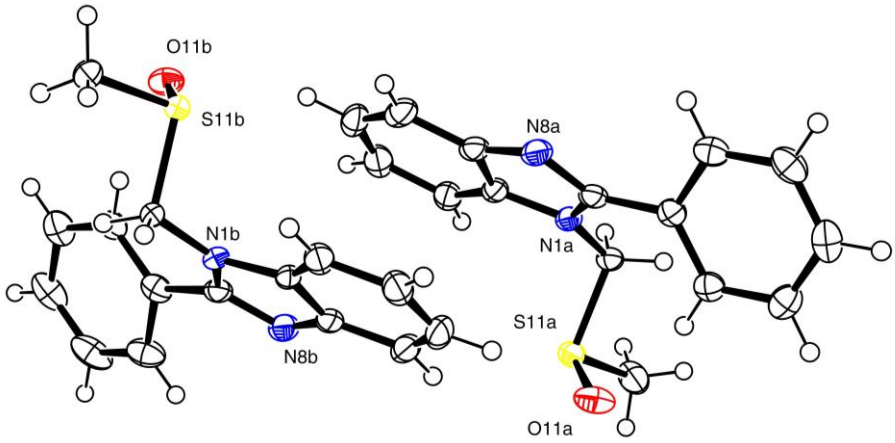


Figure 2. ORTEP diagram of product 3c (Table 3, entry 3) (CCDC 780781) showing both molecules in the asymmetric unit with ellipsoids at 30% probability. The solvent methanol and water molecules are not shown.

Figure 2 contains two molecules in the asymmetric unit together with five water molecules, three of which have reduced occupancy and one methanol, also with reduced occupancy. The two molecules in the asymmetric unit have similar geometries as is apparent from figure 2. In particular the angles around the N1-C and C-S11 bonds are 109.1(3) in A, -106.2(3) in B and -69.9(2) in A, 74.2(2)^o in B respectively thus showing that the molecules are opposite enantiomers. The phenyl rings in the two structures stack with the six C...C distances ranging from 3.54 to 3.75Å. The angle between the two phenyl ring planes is 2.3 (1)^o. There is, therefore, definite evidence of pi-stacking in this molecule.

Conclusion

In conclusion, a straightforward method for N-methylthiomethylation of benzimidazoles has been described under moderate reaction conditions. Relatively moderate reaction condition, a wide range of substrate affordability and high yields are the major advantages of this methodology. Further, chemoselective oxidation of these N-methylthiomethylbenzimidazoles to

sulfoxides has been achieved using $NaBiO_3$ in acetic acid medium. This is the first report of synthesis of this kind of sulfoxide which can be expected to open a new arena of research for synthetic organic chemists.

Experimental Section

General. All the chemicals were purchased from Aldrich Chemical Company and Spectrochem, Pvt. Ltd. (Mumbai, India). Silica Gel G with binder from Spectrochem, Pvt. Ltd. Mumbai, India was used for thin layer chromatography. ^1H and ^{13}C NMR spectra were obtained on Bruker 300 MHz instrument at 300 and 75 MHz respectively. $CDCl_3$ was purchased from Aldrich Chemical Company and d_6-DMSO from CIL. Melting points were determined on an electrical melting point apparatus with an open capillary and are uncorrected. IR spectra were recorded on a Perkin Elmer Spectrophotometer RX / FT-IR system. The C-H-N analyses were carried out on a 2400series II CHNS Analyzer, Perkin Elmer (USA). Ion cyclotron resonance Fourier transform HRMS was performed on a Micromass ZQ instrument (Waters) (location: Indian Institute of Chemical Biology, 4, Raja S. C. Mullick Road, Kolkata-700032) and ESIMS of the compounds were recorded on a Waters LC-MS-MS (quattro micro mass) instrument (Chemgen Pharma International Pvt. Ltd., Dr. Siemens Street, Block GP, Sector-V, Salt Lake City, Kolkata-700091).

Preparation of N-methylthiomethylbenzimidazoles. In a round bottomed flask (10 mL), benzimidazoles (1 mmol), N-methylpiperazine (2 mmol) and dry DMSO (2 mL) were mixed and heated on oil bath for stipulated time (monitored by TLC). After the completion of the reaction, the solvent was removed under reduced pressure in a rotary evaporator. The concentrated crude product was separated by column chromatography using silica gel (60–120 mesh) and petroleum ether (60-80 ºC) / ethyl acetate as eluant. The characteristic data for all the new compounds are given below.

2,5-Dimethyl-1-methylsulphanylmethyl-1*H*-benzimidazole (2e, Table 2, entry 5). Mixture of two tautomers**;** colorless semisolid**;** ^1H NMR (300 MHz, $CDCl_3$): δ (1.86 and 1.82) (two s, 3H), (2.31 and 2.28) (two s, 3H), 2.43 (s, 3H), 4.89 (s, 2H), 6.89 (d, J = 8.1 Hz, 1H), (6.98 and 7.30) (two s, 1H, tautomeric and aromatic), (7.07 and 7.38) (two d, J = 8.1 Hz, 1H, tautomeric and aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 14.1, 21.3, 21.6, 45.8, 46.0, 108.9, 109.4, 118.4, 118.8, 123.6, 123.6, 131.8, 132.2, 132.9, 135.0, 140.1, 142.3, 150.8, 151.3; ESI-MS (*m/z*): 207.0 (M^++1); IR (neat, cm^{-1}): 682, 852, 1090, 1276, 1380, 1463, 1532, 2376, 2909 cm^{-1}; Anal. Calc. for $C_{11}H_{14}N_2S$: C 64.04, H 6.84, N 13.58; Found: C 63.94, H 6.90, N 13.62%.

1-Methylsulphanylmethyl-2,5,6-trimethyl-1*H*-benzimidazole (2f, Table 2, entry 6). Colorless solid; m.p: 112 – 114 °C (EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 2.02 (s, 3H), 2.33 (s, 3H), 2.36 (s, 3H), 2.59 (s, 3H), 5.05 (s, 2H), 7.12 (s, 1H), 7.42 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 14.1, 20.1, 20.4, 46.0, 109.8, 119.3, 130.9, 131.2, 133.4, 140.9, 150.5; ESI-MS (*m/z*): 221.1 (M^++1); HRMS (*m/z)* for $C_{12}H_{16}N_2S$; calcd 220.1034, found 220.1032**;** IR (KBr, cm^{-1}): 675, 847,

990, 1291, 1389, 1453, 1521, 2372, 2919 cm^{-1}; Anal. Calc. for $C_{12}H_{16}N_2S$: C 65.41, H 7.32, N 12.71; Found: C 65.29, H 7.40, N 12.75.

1-Methylsulphanylmethyl-2-phenyl-1*H*-benzimidazole (2g, Table 2, entry 7). Pale yellow solid; m.p: 156 – 158 °C (EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 1.91 (s, 3H), 5.24 (s, 2H), 7.34 – 7.28 (m, 2H), 7.51 – 7.49 (m, 4H), 7.86 - 7.74 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.6, 47.3, 110.8, 119.9, 122.9, 123.0, 128.7, 129.5, 129.7, 129.9, 134.9, 142.7, 153.7; ESI-MS (m/z): 255.0 (M^++1); HRMS (m/z) for $C_{15}H_{14}N_2S$; calcd 254.0878, found 254.0876**;** IR (KBr, cm^{-1}): 750, 1000, 1077, 1151, 1277, 1365, 1447, 2374, 2920, 2993, 3047 cm^{-1}; Anal. Calc. for $C_{15}H_{14}N_2S$: C 70.83, H 5.55, N 11.01; Found: C 70.71, H 5.65, N 11.03.

5-Methyl-1-methylsulphanylmethyl-2-phenyl-1*H*-benzimidazole (2h, Table 2, entry 8). Mixture of two tautomers**;** yellow solid; m.p: 72 - 74 °C (EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 1.91 (s, 3H), (2.52 and 2.49) (two s, 3H), 5.24 (s, 2H), 7.15 (d, *J* = 8.1 Hz, 1H), (7.31 and 7.62) (two d, *J* = 0.6 Hz, 1H, tautomeric and aromatic), (7.40 and 7.71) (two d, *J* = 8.2 Hz, 1H, tautomeric and aromatic), 7.56 – 7.47 (m, 3H), 7.82 – 7.52 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.6, 21.5, 21.8, 47.2, 47.4, 110.4, 110.7, 119.4, 119.6, 124.6, 128.8, 129.5, 129.6, 129.7, 129.9, 128.0, 132.8, 133.0, 133.1, 135.1, 140.8, 142.9, 153.2, 153.6; ESI-MS (m/z): 269.2 (M^++1); IR (KBr, cm^{-1}): 701, 780, 800, 1278, 1382, 1444, 1620, 2321, 1922, 3060 cm^{-1}; Anal. Calc. for $C_{16}H_{16}N_2S$: C 71.61, H 6.01, N 10.44; Found: C 71.54, H 6.05, N 10.47.

5,6-Dimethyl-1-methylsulphanylmethyl-2-phenyl-1*H*-benzimidazole (2i, Table 2, entry 9). White crystalline solid; m.p; 82 – 84 °C (EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 1.91 (s, 3H), 2.39 (s, 3H), 2.42 (s, 3H), 5.24 (s, 2H), 7.29 (s, 1H), 7.52 - 7.49 (m, 3H), 7.58 (s, 1H), 7.76 – 7.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 20.2, 20.6, 47.3, 111.0, 120, 128.7, 129.5, 129.7, 130.1, 131.8, 132.2, 133.5, 141.6, 153.1; ESI-MS (m/z): 283.1 (M^++1); HRMS (m/z) for $C_{17}H_{18}N_2S$; calcd 282.1191, found 282.1201; IR (KBr, cm^{-1}): 701, 847, 999, 1072, 1177, 1280, 1383, 1461, 1627, 2330, 2923 cm^{-1}; Anal. Calc. for $C_{17}H_{18}N_2S$: C 72.30, H 6.42, N 9.92; Found: C 72.19, H 6.49, N 9.96.

2-(4'-Chlorophenyl)-1-methylsulphanylmethyl-1*H*-benzimidazole (2j, Table 2, entry 10). Colorless crystalline solid; m.p: 100 – 102 °C (EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 2.00 (s, 3H), 5.26 (s, 2H), 7.38 – 7.32 (m, 2H), 7.53 (td, *J* = 6.6 and 1.8 Hz, 3H), 7.77 (td, *J* = 8.4 and 2.0 Hz, 2H), 7.85 – 7.81 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.9, 47.4, 110.7, 120.1, 123.1, 123.3, 128.5, 129.2, 130.9, 135.3, 136.3, 143.0, 152.6; ESI-MS (m/z): 289.0 (M^++1); HRMS (m/z) for $C_{15}H_{13}ClN_2S$; calcd 288.0488, found 288.0482**;** IR (KBr, cm^{-1}): 740, 1049, 1089, 1182, 1242, 1346, 1529, 2374, 2866, 2922, 3090 cm^{-1} Anal. Calc. for $C_{15}H_{13}ClN_2S$: C 62.38, H 4.45, N 9.70; Found: C 62.22, H 4.55, N 9.76

1-Methylsulphanylmethyl-2-(4'-nitrophenyl)-1*H*-benzimidazole (2k, Table 2, entry 11). Yellow solid; m.p: 164 – 166 °C (EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 2.04 (s, 3H), 5.33 (s, 2H), 7.47 – 7.38 (m, 2H), 7.62 – 7.58 (m, 1H), 7.90 - 7.86 (m, 1H), 8.12 (d, *J* = 8.4 Hz, 2H), 8.41 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.1, 48.0, 111.1, 119.9, 124.2, 124.2, 124.6, 130.8, 134.8, 135.1, 141.4, 148.9, 150.5; ESI-MS (m/z): 300.0 (M^++1); HRMS (m/z) for $C_{15}H_{13}N_3O_2S$; calcd 299.0728, found 299.0726; IR (KBr, cm^{-1}): 746, 855, 1281, 1340, 1452,

1521, 2210, 2923 cm^{-1}; Anal. Calc. for $C_{15}H_{13}N_3O_2S$: C 60.18, H 4.38, N 14.04; Found: C 60.10, H 4.46, N 14.04.

2-(4'-N,N-dimethylaminophenyl)-1-methylsulphanylmethyl-1*H*-benzimidazole (2l, Table 2, entry 12). Colorless crystalline solid; m.p: 150 – 152 °C (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.98 (s, 3H), 3.03 (s, 6H), 5.29 (s, 2H), 6.79 (d, *J* = 9.0 Hz, 2H), 7.32 – 7.26 (m, 2H), 7.51 - 7.46 (m, 1H), 7.70 (d, *J* = 9.0 Hz, 2H), 7.84 – 7.79 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.7, 40.1, 47.6, 110.6, 111.8, 115.8, 119.1, 122.6, 122.9, 130.6, 134.8, 141.9, 151.4, 154.4; ESI-MS (m/z): 298.0 (M^++1); HRMS (m/z) for $C_{17}H_{19}N_3S$; calcd 297.1300, found 297.1290**;** IR (KBr, cm^{-1}): 743, 816, 940, 1062, 1185, 1277, 1367, 1483, 1608, 2376, 2918 cm^{-1}; Anal. Calc. for $C_{17}H_{19}N_3S$: C 68.65, H 6.44, N 14.13; Found: C 68.57, H 6.46, N 14.19.

2-(3',4'-Dimethoxyphenyl)-1-methylsulphanylmethyl-1*H*-benzimidazole (2m, Table 2, entry 13). Pale yellow solid; m.p: 94 – 96 °C (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.98 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 5.28 (s, 2H), 6.93 (d, *J* = 8.1 Hz, 1H), 7.30 – 7.25 (m, 2H), 7.35 (d, *J* = 8.6 Hz, 1H), 7.41 (s, 1H), 7.50 – 7.46 (m, 1H), 7.78 – 7.75 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.0, 47.9, 56.0, 56.3, 110.9, 111.2, 112.8, 119.0, 120.4, 122.6, 123.6, 123.7, 134.5, 140.3, 149.4, 151.1, 153.0; ESI-MS (m/z): 315.1 (M^++1); IR (KBr, cm^{-1}): 745, 1021, 1142, 1260, 1451, 1605, 2374, 2925 cm^{-1}; Anal. Calc. for $C_{17}H_{18}N_2O_2S$: C 64.94, H 5.77 N 8.91; Found: C 64.83, H 5.85, N 8.94.

2-(3',4'-Dimethoxyphenyl)-5,6-dimethyl-1-methylsulphanylmethyl-1*H*-benzimidazole (2n, Table 2, entry 14). Pale yellow solid; m.p: 96– 98 °C (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.02 (s, 3H), 2.38 (s, 3H), 2.42 (s, 3H), 3.90 (s, 3H), 3.94 (s, 3H), 5.24 (s, 2H), 6.98 (d, *J* = 8.2 Hz, 1H), 7.26 (s, 1H), 7.33 (dd, *J* = 8.2 and 1.8 Hz, 1H), 7.38 (d, *J* = 2.4 Hz, 1H), 7.56 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.8, 20.2, 20.7, 47.5, 56.0, 56.1, 110.8, 111.1, 112.7, 119.9, 122.3, 122.6, 131.8, 132.2, 133.8, 141.5, 149.2, 150.4, 153.1; ESI-MS (m/z): 343.1 (M^++1); IR (KBr, cm^{-1}): 1020, 1141, 1261, 1379, 1458, 1602, 2372, 2853, 2924 cm^{-1}; Anal. Calc. for $C_{19}H_{22}N_2O_2S$: C 66.64, H 6.48, N 8.18; Found: C 66.54, H 6.55, N 8.21.

5,6-Dimethyl-2-(4'-methoxyphenyl)-1-methylsulphanylmethyl-1*H*-benzimidazole (2o, Table 2, entry 15). Pale yellow solid; m.p: 102 – 104 °C (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.94 (s, 3H), 2.39 (s, 3H), 2.42 (s, 3H), 3.88 (s, 3H), 5.23 (s, 2H), 7.03 (td, *J* = 8.7, and 2.3 Hz, 2H), 7.27 (s, 1H), 7.56 (s, 1H), 7.72 (td, *J* = 8.7 and 2.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.6, 20.2, 20.6, 47.3, 55.4, 110.9, 114.2, 119.9, 122.4, 131.0, 131.8, 132.0, 133.6, 141.5, 153.1, 160.8; ESI-MS (m/z): 313.1 (M^++1); IR (KBr, cm^{-1}): 847, 1030, 1175, 1243, 1457, 1606, 2850, 2923 cm^{-1}; Anal. Calc. for $C_{18}H_{20}N_2OS$: C 69.20, H 6.45, N 8.97; Found: C 69.12, H 6.48, N 9.02.

2-(4'-Chlorophenyl)-5,6-dimethyl-1-methylsulphanylmethyl-1*H*-benzimidazole (2p, Table 2, entry 16). Colourless crystalline solid; m.p: 178 – 180 °C (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.95 (s, 3H), 2.38 (s, 3H), 2.43 (s, 3H), 5.26 (s, 2H), 7.31 (s, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.57 (s, 1H), 7.77 (d, *J* = 8.4Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.7, 20.2, 20.7, 42.8, 111.2, 119.0, 126.7, 129.3, 130.5, 131.0, 132.9, 133.2, 133.5, 136.9. 150.7; ESI-MS (m/z): 317.0 (M^++1); HRMS (m/z) for $C_{17}H_{17}ClN_2S$; calcd 316.0801, found 316.0793**;** IR (KBr, cm^{-1}): 843,

1000, 1087, 1288, 1319, 1461, 2376, 2921 cm^{-1}; Anal. Calc. for $C_{17}H_{17}ClN_2S$: C 64.44, H 5.41, N 8.84; Found: C 64.33, H 5.50, N 8.86.

2-(4'-Bromophenyl)-5,6-dimethyl-1-methylsulphanylmethyl-1*H*-benzimidazole (2q, Table 2, entry 17). Colourless crystalline solid; m.p**:** 182 – 184 °C (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.95 (s, 3H), 2.38 (s, 3H), 2.42 (s, 3H), 5.22 (s, 2H), 7.29 (s, 1H), 7.56 (s, 1H), 7.70-7.63 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.8, 20.2, 20.7, 47.8, 111.3, 119.0, 125.3, 127.1, 131.1, 132.3, 132.9, 133.3, 133.6, 150.8; ESI-MS (m/z): 361.0 (M^++1); HRMS (*m/z*) for $C_{17}H_{17}BrN_2S$: calcd 360.0296, found 360.0302**;** IR (KBr, cm^{-1}): 840, 1000, 1067, 1286, 1400, 1463, 1595, 2464, 2858, 2922 cm^{-1}; Anal. Calc. for $C_{17}H_{17}BrN_2S$: C 56.51, H 4.74, N 7.75; Found: C 56.39, H 4.83, N 7.78.

5,6-Dimethyl-2-(4'-N,N-dimethylaminophenyl)-1-methylsulphanylmethyl-1*H*-benzimidazole (2r, Table 2, entry 18). Pale yellow solid; m.p**:** 156 – 158 °C (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.96 (s, 3H), 2.42 (s, 3H), 2.47 (s, 3H), 3.04 (s, 6H), 5.27 (s, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 7.26 (s, 1H), 7.58 (s, 1H), 7.68 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 20.2, 20.6, 40.1, 47.4, 110.9, 111.8, 116.4, 119.3, 130.5, 131.7, 133.4, 140.8, 151.2, 153.7; ESI-MS (*m/z*): 326.1 (M^++1); IR (KBr, cm^{-1}): 740, 1049, 1089, 1182, 1242, 1346, 1529, 2374, 2866, 2922, 3090 cm^{-1}; Anal. Calc. for $C_{19}H_{23}N_3S$: C 70.11, H 7.12, N 12.91; Found: C 69.99, H 7.21, N 12.94.

2-(1*H*-Benzimidazol-2-yl)-1-methylsulphanylmethyl-1*H*-benzimidazole (2s, Table 2, entry 19). White solid; m.p: 200 - 202 °C (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.17 (s, 3H), 6.45 (s, 2H), 7.33 – 7.19 (m, 4H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 8.7 Hz, 2H), 7.88 (d, *J* = 7.8 Hz, 1H), 14.30 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 47.5, 111.7, 111.9, 119.6, 120.3, 122.7, 123.9, 124.3, 124.4, 134.0, 135.5, 142.0, 143.3, 143.5, 143.9; ESI-MS (*m/z*): 295.0 (M^++1); IR (KBr, cm^{-1}): 767, 1034, 1241, 1356, 1453, 2356, 2907, 2990, 3040 cm^{-1}; Anal. Calc. for $C_{16}H_{14}N_4S$: C 65.28, H 4.79, N 19.03; Found: C 65.21, H 4.86, N 19.04.

Preparation of sulfoxides. In a round bottomed flask (20 mL), sulfide (1 mmol), $NaBiO_3$ (3 mmol), aqueous acetic acid (4 mL, 50% v/v) and acetone (1 mL) were mixed and refluxed for stipulated time (monitored by TLC). After the completion of the reaction, the reaction mixture was filtered through a pad of celite and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 10 mL). The EtOAc extract was washed with sodium carbonate solution (3 x 10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was separated by column chromatography using silica gel (60–120 mesh) and ethyl acetate-petroleum ether (60-80 ºC) as eluant. The characteristic data for the compounds are given below.

2-Methyl-1-methanesulphinylmethyl-1*H*-benzimidazole (3a, Table 3, entry 1). Pale yellow solid; m.p: 186 – 188 °C (MeOH and EtOAc); ^{1}H NMR (300 MHz, d_6-DMSO): δ 2.56 (s, 3H), 2.68 (s, 3H), 5.44 (d, *J* = 13.8 Hz, 1H), 5.59 (d, *J* = 13.8 Hz, 1H), 7.20 – 7.15 (m, 2H), 7.53 – 7.50 (m, 1H), 7.61 – 7.58 (m, 1H); ^{13}C NMR (75 MHz, d_6-DMSO): δ 14.0, 36.1, 62.5, 110.6, 118.5, 122.0, 122.1, 135.3, 142.3, 153.1; ESI-MS (*m/z*): 209.0 (M^++1); IR (KBr, cm^{-1}): 856,

1080, 1376, 1465, 1543, 2374, 2928, 2995 cm^{-1}; Anal. Calc. for $C_{10}H_{12}N_2OS$: C 57.67, H 5.81 N 13.45; Found: C 57.58, H 5.88, N 13.47.

1-Methanesulphinylmethyl-2,5,6-trimethyl-1*H*-benzimidazole (3b, Table 3, entry 2). Pale yellow solid; m.p: 72 – 74 °C (MeOH and EtOAc); ^{1}H NMR (300 MHz, d_6-DMSO): δ 2.24 (s, 3H), 2.26 (s, 3H), 2.51 (s, 3H), 2.71 (s, 3H), 5.36 (d, *J* = 14.1 Hz, 1H), 5.52 (d, *J* = 14.1 Hz, 1H), 7.28 (s, 2H), 7.37 (s, 1H); ^{13}C NMR (75 MHz, d_6-DMSO): δ 14.0, 19.9, 20.18, 36.1, 62.7, 110.8, 118.7, 130.3, 130.5, 133.8, 140.8, 152.1; ESI-MS (*m/z*): 237.0 (M^++1); HRMS (*m/z*) for $C_{12}H_{16}N_2OS$; calcd 236.0983, found 236.0973**;** IR (KBr, cm^{-1}): 846, 1050, 1398, 1465, 1527, 2371, 2919, 2974 cm^{-1}; Anal. Calc. for $C_{12}H_{16}N_2OS$: C 60.99, H 6.82, N 11.85; Found: C 6O.87, H 6.91, N 11.88.

1-Methanesulphinylmethyl-2-phenyl-1*H*-benzimidazole (3c, Table 3, entry 3). Colorless crystalline solid; m.p: 68 – 70 °C (MeOH and EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.42 (s, 3H), 5.08 (d, *J* = 13.5 Hz, 1H), 5.19 (d, *J* = 13.5 Hz, 1H), 7.31 – 7.22 (m, 2H), 7.50 – 7.47 (m, 4H), 7.77 – 7.69 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.6, 64.6, 110.6, 119.7, 123.3, 123.5, 128.7, 129.8, 130.1, 135.1, 142.3, 153.7; ESI-MS (*m/z*): 271.0 (M^++1); IR (KBr, cm^{-1}): 753, 1037, 1392, 1458, 2184, 3191 cm^{-1}; Anal. Calc. for $C_{15}H_{14}N_2OS$: C 66.64, H 5.22, N 10.36; Found: C 66.56, H 5.26, N 10.40.

5-Methyl-1-methanesulphinylmethyl-2-phenyl-1*H*-benzimidazole (3d, Table 3, entry 4). Mixture of two tautomers**;** pale yellow solid; m.p: 68 – 70 °C (MeOH and EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ (2.46 and 2.49) (two s, 3H, tautomeric), 2.51 (s, 3H), 5.30 – 5.13 (m, 2H), (7.13 and 7.63) (two d, *J* = 8.1 and 8.4 Hz, 2H, tautomeric and aromatic), (7.34 and 7.53) (two s, 1H, tautomeric and aromatic), 7.52 – 7.40 (m, 3H), 7.80 – 7.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4, 21.8, 36.9, 64.9, 110.5, 110.7, 119.3, 119.3, 125.4, 125.5, 128.2, 128.5, 129.0, 129.0, 130.0, 130.0, 130.4, 130.6, 133.0, 133.9, 134.2, 135.3, 139.9, 141.7, 153.1, 153.5; ESI-MS (*m/z*): 285.0 (M^++1); IR (KBr, cm^{-1}): 774, 1082, 1397, 1478, 1522, 2284, 2996 cm^{-1}; Anal. Calc. for $C_{16}H_{16}N_2OS$: C 67.58, H 5.67, N 9.85; Found: C 67.49, H 5.72, N 9.89.

2-(4'-Chlorophenyl)-1-methanesulphinylmethyl-1*H*-benzimidazole (3e, Table 3, entry 5). Colorless crystalline solid; m.p: 94 – 96 °C (MeOH and EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$ + three drops of d_6-DMSO): δ 2.49 (s, 3H), 5.04 (d, *J* = 13.5 Hz, 1H), 5.15 (d, *J* = 13.5 Hz, 1H), 7.27 – 7.19 (m, 2H), 7.44 – 7.34 (m, 3H), 7.71 – 7.66 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ + three drops of d_6-DMSO): δ 36.7, 64.6, 110.5, 119.7, 123.4, 123.5, 127.2, 128.8, 131.2, 135.0, 136.3, 142.2, 152.7; ESI-MS (*m/z*): 305.0 (M^++1); HRMS (*m/z*) for $C_{15}H_{13}ClN_2OS$; calcd 304.0437, found 304.0435; IR (KBr, cm^{-1}): 741, 1045, 1246, 1380, 1407, 1459, 1603, 2377, 2919, 2996, 3054 cm^{-1}; Anal. Calc. for $C_{15}H_{13}ClN_2OS$: C 59.11, H 4.30, N 9.19; Found: C 59.02, H 4.37, N 9.21.

1-Methanesulphinylmethyl-2-(4'-nitrophenyl)-1*H*-benzimidazole (3f, Table 3, entry 6). Yellow solid; m.p: 212 – 214 °C (MeOH and EtOAc)**;** ^{1}H NMR (300 MHz, d_6-DMSO): δ 2.72 (s, 3H), 5.50 (d, *J* = 14.1 Hz, 1H), 5.64 (d, *J* = 14.1 Hz, 1H), 7.38 – 7.30 (m, 2H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.81 (d, *J* = 7.5 Hz,1H), 8.20 (d, *J* = 8.4 Hz, 2H), 8.35 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, d_6-DMSO,): δ 36.3, 63.6, 112.1, 119.8, 123.4, 123.7, 123.8, 135.5, 135.8, 135.9,

142.5, 148.1, 152.0; ESI-MS (*m/z*): 316.3 (M^++1); IR (KBr, cm^{-1}): 746, 857, 1052, 1343, 1512, 1599, 2448, 2922 cm^{-1}; Anal. Calc. for $C_{15}H_{13}N_3O_3S$: C 57.13, H 4.16, N 13.33; Found: C 56.99, H 4.25, N 13.38.

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