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SYNTHESIS AND SPECTRAL CHARACTERIZATION OF 2-MERCAPTOBENZIMIDAZOLE DERIVATIVES USING A NEW ACTIVE PHASE TRANSFER REAGENT UNDER PTC CONDITIONS

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Abstract : The phase transfer catalyzed synthesis of 2-Mercaptobenzimidazole derivatives using the new active phase transfer reagent namely, 2-benzilidine-N,N,N,N',N',N'-hexaethyl propane-1,3-diammonium dibromide (Dq-Br) have been described. The structures of all the fifteen compounds have been established by spectroscopic means.

Phase Transfer Catalysis (PTC) has been well-established as a most effective tool in solving the immiscibility problems associated with aqueous-organic biphase reaction systems[1-3]. The most commonly used PTCs are quaternary ammonium and phosphonium salts. The advantages of PTC, include fast reaction rates at mild experimental conditions, high product selectivity, moderate operating temperatures, savings on expensive anhydrous aprotic solvents, use of aqueous

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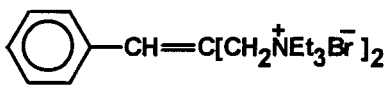
sodium or potassium hydroxide instead of alkali metal alkoxide and the ease of applicability on industrial scale production.

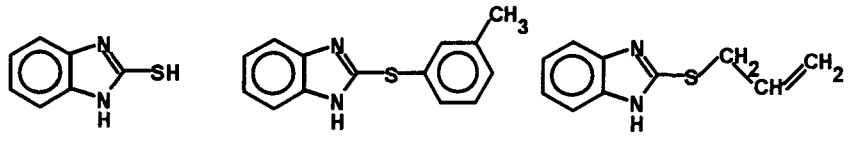
2-Mercaptobenzimidazole derivatives having substituents at either the nitrogen or sulfur in a thioamide ring are reported to exhibit a broad spectrum of biological activity4-10. Earlier studies11-12 on the preparation of 2-Mercaptobenzimidazole derivatives reveal the use of expensive polar aprotic solvents, strictly anhydrous with high temperature conditions and long reaction times. However, the method employing PTC enabled to obtain higher yields under mild conditions with relatively shorter reaction times.

We have synthesized and characterized a novel phase transfer reagent viz., 2-benzilidine-N,N,N,N',N',N'-hexaethylpropane-1,3-diammonium dibromide (Dq-Br) and studied its utility in simple dichlorocarbene addition to Olefins. High yields of products were obtained using the new Dq-Br. A detailed procedure for the synthesis of Dq-Br are discussed in the preceding paper.



Dq-Br

In continuation of our studies related to the utility of a new active phase transfer reagent, we report the synthesis and spectral characterization of 2-mercaptobenzimidazole derivatives from compound A, B and C using the new active phase transfer reagent (Dq-Br). The derivatives have been prepared under two sets of conditions: one set resulted in substitution at the nitrogen atom while the other set yielded S-substituted compounds.



A B C

The results shown in Table 1. establish the utility of the new Dq-Br for the synthesis of 2-mercaptobenzimidazole derivatives. In the absence of the catalyst, all N-alkylations resulted in less than 20% conversions and all S-alkylations gave less than 35% (except S.No. 15, which case no reaction occurred). The phase transfer catalyzed synthesis of 2-mercaptobenzimidazole derivatives resulted in higher yields at shorter reaction times, easy reaction work-up and besides the reaction conditions were mild.

EXPERIMENTAL

General : ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a BRUKER-AM-400 NMR Spectrometer with TMS as an internal standard. Mass Spectra were obtained on a JEOL JMS-100 Mass Spectrometer at ionization potential, 12 eV. The infrared spectra were measured on a PERKIN-ELMER model 983 IR Spectrometer. Liquid Chromatography was carried out using Shimadzu LC-9A instrument.

General Procedure for the S-Alkylation of 2-Mercaptobenzimidazole (A) :

A 150 ml three-necked round-bottomed flask was fitted with flat-bladed stirring paddle and a reflux condenser. 2-Mercaptobenzimidazole, 1.0 g (0.0066 mol),

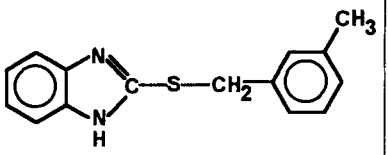
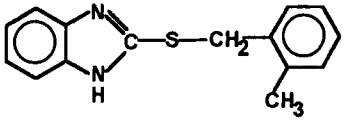
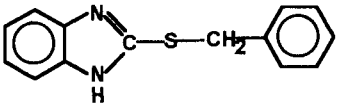
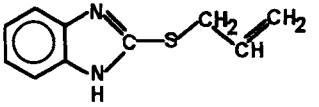
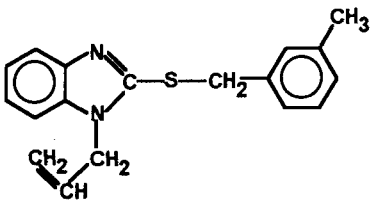
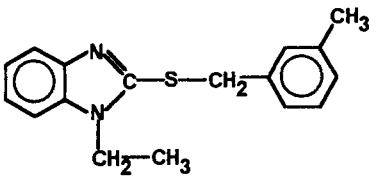
KOH, 0.6 g dissolved in 50 ml H_2O, 96.34 mg of Dq-Br (3 mol% based on the substrate amount) and 50 ml dichloromethane were placed in the flask. The ingredients were conditioned for 10 minutes with the thermostat set at 30°C. Alkyl bromide (1.2 g) preheated to 30°C was added to the reaction mixture and stirred at 1000 rpm. Samples were collected from the organic layer at regular intervals of time and were analyzed using HPLC model LC 9A (Shimadzu) having an absorbance detector (254 nm, SPD-6A) and column, Merck RP-8 (5 μm). The eluent was acetonitrile/water = 50 : 50 with flow rate 1.2 ml/min.

The reaction mixture was washed repeatedly with water and dried over anhydrous magnesium sulfate. Ethanol (100 ml) was added to the crude product after removal of the solvent. The ethanolic solution was reduced to half of its volume over water bath. Upon slow addition of deionized water to the cold ethereal solution, the product crystallized. The pure product was filtered and dried. The spectral data were in agreement with the expected product.

General procedure for the N-Alkylation of 2-*m*-Xylene sufanyl-1*H*-benzoimidazole (B) :

A 150 ml three-necked round-bottomed flask was charged with 50 ml dichloromethane, compound B, 0.5 g (0.0019 mol), KOH, 0.6 g dissolved in 50 ml H_2O and 96.92 mg of Dq-Br (10 mol% based on the substrate amount). The contents were conditioned for 10 minutes with the thermostat maintained at 30°C. Alkyl bromide (allyl bromide / benzyl bromide = 0.8 g ; ethyl bromide/ 1-bromo propane/ 2-bromo propane/ n-butyl bromide were taken in excess) pre-heated to

Table 1 : Synthesis of 2- Mercaptobenzimidazole derivatives using a new DQ-Br under PTC Conditions.

S.No	Substrate	RBr	Product	Time, h	%Conv.[a]
1.	**A**	α-bromo-*m*-xylene		2	90
2.	**A**	α-bromo-*o*-xylene		2	93
3.	**A**	Benzyl bromide		2	70
4.	**A**	Allyl bromide		1.5	96
5.	**B**	Allyl bromide		1.5	95
6.	**B**	Ethyl bromide		2.5	98

(continued)

Table 1. Continued

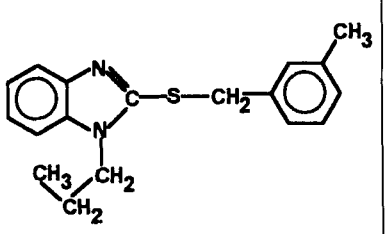
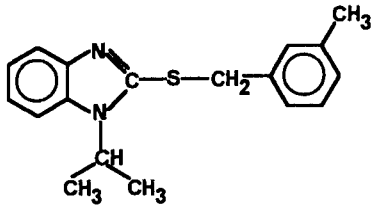
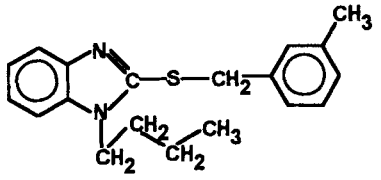
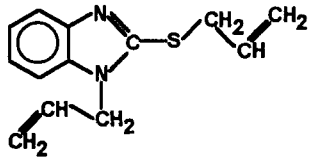
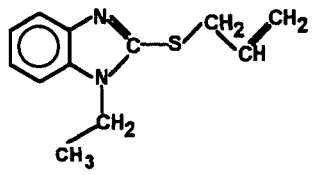
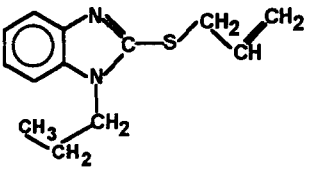
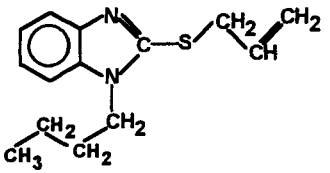
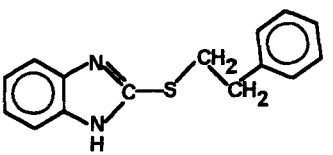
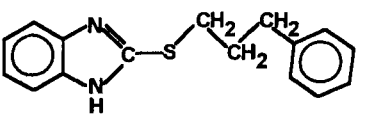
7.	**B**	n-propyl bromide		3	93
8.	**B**	Iso-propyl bromide		3	90
9.	**B**	n-butyl bromide		3	95
10.	**C**	Allyl bromide		2	97
11.	**C**	Ethyl bromide		2	95

Table 1. Continued

12.	C	n-propyl bromide		2	96
13.	C	n-butyl bromide		3	95
14.	A	(2-bromo-ethyl) benzene.		3	60
15.	A	1-bromo-3-phenyl propane		3	trace[b]

a : % conversion by HPLC, b : formed in trace amount detected by GC-MS

30°C was added to the reaction vessel and stirred at 1000 rpm. Samples were withdrawn from the organic layer at regular intervals of time and were analyzed using HPLC model LC 9A (Shimadzu) having an absorbance detector (254 nm, SPD-6A) and column, Merck RP-8 (5 μm). The eluent was acetonitrile/water = 50 : 50 with flow rate 1.2 ml/min. To the cold reaction, ether (30 ml) was added, washed repeatedly with deionized water and dried over anhydrous magnesium sulfate. The excess, low boiling alkyl bromides were also removed. The compound was purified using silica gel column chromatography. The spectral properties were in agreement with the expected products.

General procedure for the N-Alkylation of 2-Allyl sufanyl-1*H*-benzoimidazole (C) :

A 150 ml three-necked round-bottomed flask was charged with 50 ml dichloromethane, compound C, 0.1 g (0.00053 mol), KOH, 0.6 g dissolved in 50 ml H_2O and 26 mg of Dq-Br (10 mol% based on the substrate amount). The contents were conditioned for 10 minutes with the thermostat maintained at 30°C. Alkyl bromide (allyl bromide = 0.8 g ; ethyl bromide / 1-bromo propane / n-butyl bromide were taken in excess) pre-heated to 30°C was added to the reaction vessel and stirred at 1000 rpm. Samples were withdrawn from the organic layer at regular intervals of time and were analyzed using HPLC model LC 9A (Shimadzu) having an absorbance detector (254 nm, SPD-6A) and column, Merck RP-8 (5 μm). The eluent was acetonitrile/water = 50 : 50 with flow rate 1.2 ml/min. To the cold reaction, ether (30 ml) was added, washed repeatedly with deionized water and dried over anhydrous magnesium sulfate. The excess, low

boiling alkyl bromides were also removed. The compound was purified using silica gel column chromatography. The spectral properties were in agreement with the expected products.

SPECTRAL DATA

2-*m*- Xylene sufanyl-1*H*-benzoimidazole (1) :

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 7.5-7.0 (m, 9H, Aromatic, -NH), 4.5 (s, 2H, -CH_2), 2.25 (s, 3H, -CH_3). ν_{max} / cm^{-1} : 2804, 1585, 1497, 1270, 1152, 1010, 977, 786. MS (m/z) : 254 (32, M^+), 149 (14), 105(100), 77 (27).

2-*o*- Xylene sufanyl-1*H*-benzoimidazole (2) :

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 7.6-7.0 (m, 9H, Aromatic, -NH), 4.5 (s, 2H, -CH_2), 2.3 (s, 3H, -CH_3). ν_{max} / cm^{-1} : 2355, 1733, 1698, 1550, 1507, 1457, 1340, 1270, 1095, 780. MS (m/z) : 254 (32, M^+), 149 (14), 105 (100), 77 (35).

2-Benzyl sulfanyl-1*H*-benzoimidazole (3) :

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 7.5-7.1 (m, 10H, Aromatic, -NH), 4.6-4.5 (s, 2H, -CH_2). ν_{max} / cm^{-1} : 2950, 1652, 1550, 1509, 1413, 1267, 1232, 1011, 979, 748. MS (m/z) : 240 (27, M^+), 149 (13), 95 (100), 77 (4).

2-Allyl sulfanyl-1*H*-benzoimidazole (4) :

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 7.5-7.1 (m, 4H, Aromatic), 6.1 (s, 1H, -NH), 5.9 (m, 1H, -CH), 5.35-5.10 (dd, 2H, -CH_2), 3.9 (d, 2H, -CH_2). ν_{max} / cm^{-1} : 2362, 1772, 1635, 1540, 1438, 1271, 1231, 1090, 932, 740. MS (m/s) : 190 (27, M^+), 175 (74), 149 (30), 118 (14), 36 (100).

1-Allyl-2-*m*-xylene sulfanyl-1*H*-benzoimidazole (5) :

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 7.8 –7.0 (m, 8H, Aromatic), 5.8 (m, 1H, -CH), 5.20-5.0 (dd, 2H, $-CH_2$), 4.6 (s, 2H, $-CH_2$), 2.3 (s, 3H, $-CH_3$). ν_{max} / cm^{-1} : 3075, 2900, 1650, 1613, 1450, 1275, 1250, 1013, 975, 738. MS (m/z) : 294 (17, M^+), 279 (14), 261 (28), 189 (37), 105 (100), 77 (33).

1-Ethyl-2-*m*-xylene sulfanyl-1*H*-benzoimidazole (6) :

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 7.8-7.0 (m, 8H, Aromatic), 4.6 (s, 2H, $-CH_2$), 4.1 (q, 2H, $-CH_2$), 2.3 (s, 3H, $-CH_3$), 1.3 (t, 3H, $-CH_3$). ν_{max} / cm^{-1} : 3075, 2975, 1625, 1425, 1256, 1125, 900, 738. MS (m/z) : 282 (42, M^+), 249 (73), 177 (39), 163 (12), 105 (100), 77 (33).

1-Propyl-2-*m*-xylene sulfanyl-1*H*-benzoimidazole (7) :

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 7.7-7.0 (m, 8H, Aromatic), 4.6 (s, 2H, $-CH_2$), 4.0 (t, 2H, $-CH_2$), 2.3 (s, 3H, $-CH_3$), 1.8-1.7 (m, 2H, $-CH_2$), 0.9 (t, 3H, $-CH_3$). ν_{max} / cm^{-1} : 3050, 2963, 1613, 1425, 1280, 1250, 1125, 1012, 925, 738. MS (m/z) : 296 (39, M^+), 263 (38), 221 (24), 191 (27), 131 (16), 105 (100), 77 (30).

1-Isopropyl-2-*m*-xylene sulfanyl-1*H*-benzoimidazole (8) :

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 7.75-7.0 (m, 8H, Aromatic), 4.70-4.66 (m, 1H, -CH), 4.57(d, 2H, $-CH_2$), 2.30 (s, 3H, $-CH_3$), 2.30 (d, 3H, $-CH_3$), 1.55 (d, 3H, $-CH_3$). ν_{max} / cm^{-1} : 3075, 2975, 1619, 1438, 1325, 1275, 1150, 1038, 938, 738. MS (m/z) : 296 (29, M^+), 263 (50), 253 (13), 221 (27), 191 (44), 164 (22), 151 (22),105 (100), 77 (30).

1-Butyl-2-*m*-xylene sulfanyl-1*H*-benzoimidazole (9) :

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 7.8-7.1 (m, 8H, Aromatic), 4.6 (s, 2H, $-CH_2$),

4.0 (t, 2H, $-CH_2$), 2.3 (s, 3H, $-CH_3$), 1.8-1.6 (m, 2H, CH_2), 1.4-1.2 (m, 2H, $-CH_2$), 0.9 (t, 3H,$-CH_3$). ν_{max} / cm^{-1} : 3050, 2950, 1613, 1438, 1275, 1238, 1138, 875, 738. MS (m/z) : 310 (36, M^+), 277 (31), 235 (14), 221 (17), 205 (8), 173 (31), 163 (10), 105 (100), 77 (19).

1-Allyl-2-allyl sulfanyl-1*H*-benzoimidazole (10) :

^1H NMR (400 MHz, $CDCl_3$) : δ = 7.7-7.1 (m, 4H, Aromatic), 6.05 (m, 1H, -CH), 5.85 (m, 1H, -CH), 5.4-5.3 (dd, 2H, $-CH_2$), 5.1-4.9 (dd, 2H, $-CH_2$), 4.7 (d, 2H, $-CH_2$), 4.0 (d, 2H,$-CH_2$). ν_{max} / cm^{-1} : 3100, 2925, 1638, 1450, 1363, 1275, 1238, 925, 738. MS (m/z) : 230 (43, M^+), 215 (100), 197 (9), 187(10), 174 (12), 156 (14), 130 (22), 90 (9), 77 (14), 39 (27).

1-Ethyl-2-allyl sulfanyl-1*H*-benzoimidazole (11) :

^1H NMR (400 MHz, $CDCl_3$) : δ = 7.7-7.1 (m, 4H, Aromatic), 6.1-5.9 (m, 1H, -CH), 5.4-5.1 (dd, 2H, $-CH_2$), 4.2 (q, 2H, $-CH_2$), 4.0 (d, 2H, $-CH_2$), 1.4 (t, 3H, $-CH_3$). ν_{max} / cm^{-1} : 3025, 2975, 1638, 1425, 1369, 1250, 1113, 975, 738. MS (m/z) : 218 (50, M^+), 203 (100), 189 (10), 185 (15), 175 (34), 157 (15), 130 (12), 118 (15), 90 (15), 77 (12), 39 (19).

1-Propyl-2-allyl sulfanyl-1*H*-benzoimidazole (12) :

^1H NMR (400 MHz, $CDCl_3$) : δ = 7.7-7.1 (m, 4H, Aromatic), 6.0-5.9 (m, 1H, -CH), 5.3-5.0 (dd, 2H, $-CH_2$), 4.1-3.9 (m, 6H, $-CH_2$), 0.9 (t, 3H, $-CH_3$). ν_{max} / cm^{-1} : 3025, 2975, 1638, 1500, 1438, 1263, 975, 738. MS (m/z) : 232 (45, M^+), 217 (59), 199 (12), 189 (25), 175 (100), 157 (30), 150 (13), 130 (13), 118 (11), 90 (10), 77 (14), 41 (23), 39 (20).

1-Butyl-2-allyl sulfanyl-1*H*-benzoimidazole (13) :

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 7.7-7.1 (m, 4H, Aromatic), 6.0 (m, 1H, -CH), 5.4-5.1 (dd, 2H, $-CH_2$), 4.1-4.0 (m, 4H, $-CH_2$), 1.8-1.7 (m, 2H, $-CH_2$), 1.4-1.3 (m, 2H, $-CH_2$), 1.0-0.9 (t, 3H, $-CH_3$). ν_{max} / cm^{-1} : 3075, 2963, 1638, 1425, 1275, 975, 913, 725. MS (m/z) : 246 (78, M^+), 231 (62), 213 (96), 189 (67), 175 (100), 157 (28), 130 (10), 119 (15), 77 (17), 41 (42), 39 (28).

2-Ethyl benzyl sulfanyl-1*H*-benzoimidazole (14) :

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 7.50-7.0 (m, 10H, Aromatic, -NH), 3.54 (t, 2H, $-CH_2$), 3.14 (t, 2H, $-CH_2$). ν_{max} / cm^{-1} : 3050, 2950, 1600, 1486, 1450, 1275, 1213, 1050, 738. MS (m/z) : 254 (16, M^+), 150 (100), 122 (14), 105 (75), 77 (18).

3-Propyl phenyl sulfanyl-1*H*-benzoimidazole (15) :

MS (m/z) : 268 (9, M^+), 221 (77), 150 (100), 131 (14), 122 (30), 91 (94), 77 (10), 65 (32), 39 (16).

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