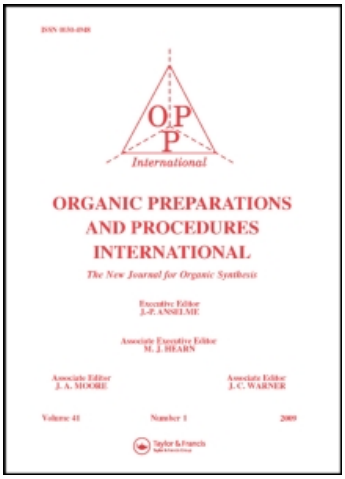

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SYNTHESIS OF 2-MERCAPTOBENZOTHIAZOLE AND OF 2-MERCAPTO-BENZIMIDAZOLE DERIVATIVES USING POLYMER-SUPPORTED ANIONS

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OPPI BRIEFS

SYNTHESIS OF 2-MERCAPTOBENZOTHIAZOLE AND OF 2-MERCAPTO-BENZIMIDAZOLE DERIVATIVES USING POLYMER-SUPPORTED ANIONS†,††

Submitted by (11/23/04)

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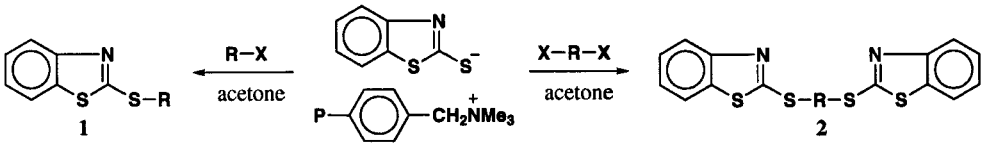
2-Mercaptobenzothiazole (MBT) and its derivatives have been used to protect copper and copper alloys against corrosion. MBT is an important vulcanization catalyst in the rubber industry. It also plays a role in analysis as a reagent for cadmium as well as for the determination of copper, lead, bismuth, silver, mercury, thallium, gold, platinum and iridium.[1] S-alkyl and S-acyl derivatives of 2-mercaptobenzothiazole were reported to possess antifungal and antibacterial activities[2] and also found to be useful in the leather industry.[3,4] 2-(Thiocyanomethylthio)benzothiazole is a potential contact fungicide for several economically important crops such as barley, cotton, corn and wheat. 2,2'-Dithiobis(benzothiazole) is used as a fungicide, insecticide, sensitizer and anti-scorching agent in vulcanization of rubber.[5]

2-Mercaptobenzimidazole (MBI) is an important chemical for many industrial applications, such as an inhibitor for copper plating, antioxidant for plating rubber compounds, adsorbent for heavy metal, antiseptic and medical substances.[6-8] MBI is used as a non-staining secondary antioxidant and antiozonant for the rubber and nylon tire cord industry. It is useful for heat resistance when used in sulfur-less vulcanization. It is also used as an intermediate in the synthesis of pharmaceuticals (*e. g. lansoprazole*) and in other organic compounds for the rubber industry. The SH group plays a significant role in biological metabolism (*e. g.* in metabolite transfer) and for this reason thiols exhibit inhibitory or accelerating effects on metabolic processes.[1] 2-Mercaptobenzimidazole derivatives having substituents at either the nitrogen or sulfur of a thioamide ring are reported to exhibit a broad spectrum of biological activity.[9-14] MBI and its derivatives have proven valuable in preventing the aging of rubber and also display insecticidal properties.[15]

However, a literature survey has revealed that the synthesis of derivatives of MBT[4, 5, 16-18] and MBI[15, 19-21] requires reflux conditions and long reaction times. Furthermore, isolation is tedious and purification is necessary. In continuation of our work,[23-25] we report herein a simple, rapid, efficient and environmentally friendly method for synthesis of MBT/MBI derivatives,

needed for a study of structure-activity relationships. Amberlite IRA-400 (chloride form) resin was used to support the MBT/MBI anion. The alkyl halides and acyl chlorides were added to the MBT/MBI anion-supported resin in acetone and the mixture was stirred until the reaction was complete to yield S-alkyl and S-acyl derivatives, respectively (*Schemes 1 & 2*). Reactions with



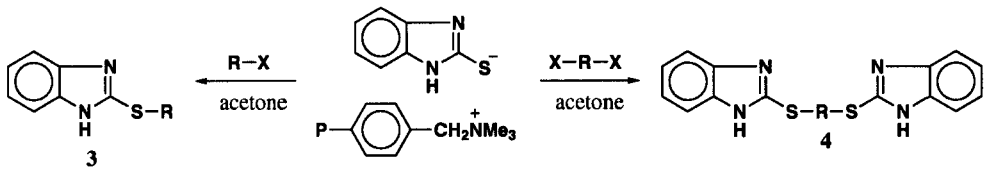
1 2

a) R = CH_3
b) R = CH_2CH_3
c) R = $CH_2CH_2CH_3$
d) R = $CH(CH_3)_2$
e) R = $CH_2CH_2CH_2Br$
f) R = $CH_2(CH_2)_2CH_3$
g) R = $CH_2CH_2CH(CH_3)_2$
h) R = $CH_2CH(CH_3)CH_2CH_3$
i) R = $CH_2CH{=}CH_2$
j) R = $CH_2C_6H_5$
k) R = $COCH_3$
l) R = COC_6H_5
m) R = $COCH_2C_6H_5$
n) R = $COCH{=}CHC_6H_5$
o) R = $COOCH_2CH_3$
p) R = $COOCH_2C_6H_5$

a) R = $-CH_2CH_2-$, X = Br
b) R = $-CH_2CH_2CH_2-$, X = Br
c) R = -COCO-, X = Cl
d) R = $-COCH_2CO-$, X = Cl
e) R = $-CO(CH_2)_2CO-$, X = Cl
f) R = $-CO(CH_2)_4CO-$, X = Cl

Scheme 1

α,ω-dibromoalkanes and diacyl chlorides gave dithioethers and dithioesters dimer derivatives (*Schemes 1 & 2*). Furthermore, reaction of polymer-supported S-alkylated products of MBI with



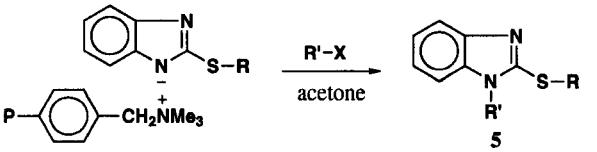
3 4

a) R = CH_3
b) R = CH_2CH_3
c) R = $CH_2CH_2CH_3$
d) R = $CH_2CH_2CH_2Br$
e) R = $CH_2(CH_2)_2CH_3$
f) R = $CH_2CH{=}CH_2$
g) R = $CH_2C_6H_5$
h) R = CH_2COOH
i) R = $COCH_3$
j) R = COC_6H_5

a) R = $-CH_2CH_2-$, X = Br
b) R = $-CH_2CH_2CH_2-$, X = Br
c) R = $-CH_2(CH_2)_2CH_2-$, X = Br

Scheme 2

alkyl halides yielded S,N-dialkylated products (*Scheme 3*). The compounds were characterized by their physical constants in comparison with literature data. All newly synthesized compounds were characterized by ^1H NMR spectroscopic method and elemental analysis.



5

a) R = R' = $CH_2(CH_2)_2CH_3$, X = Br; b) R = R' = $CH_2CH{=}CH_2$, X = Br; c) R = R' = $CH_2C_6H_5$, X = Br

Scheme 3

EXPERIMENTAL SECTION

All chemicals were of analytical grade and acetone was freshly distilled prior to use. Commercial Amberlite IRA-400 (chloride form) resin was activated by treatment with 5N HCl solution before use. The reactions were monitored by TLC on silica gel TLC using pet. ether:chloroform (8:2) and chloroform:acetone (9:1 and 8:2) solvent mixture. Melting points and boiling points are uncorrected.

General Procedure for Supporting MBT and MBI anion on Amberlite IRA-400.- MBT/MBI (100 mmoles) was dissolved in 100 mL of an aqueous solution of sodium hydroxide (100 mmoles). The activated Amberlite IRA-400 (chloride form, 100 g) was packed into a column (2 cm diameter and 45 cm length) and the above solution of sodium salt of MBT/MBI was eluted slowly dropwise (1.5 mL/min). Thereafter, the resin was washed with distilled water until complete removal of chloride ions and excess of MBT/MBI anion. It was then washed with ethanol followed by acetone and dried *in vacuo* at 50°C for 3 hr. Similarly 2-butylthiobenzimidazole, 2-allylthiobenzimidazole and 2-benzylthiobenzimidazole were supported on the resin using KOH instead of NaOH.

The exchange capacity of the MBT/MBI anion supported resin was determined by passing aqueous 1N NaCl (100 mL) solution through the supported resin (1 g) packed in a column. The MBT/MBI anion in the eluent was titrated against 0.01 N HCl using methyl orange as an indicator. The exchange capacity of the supported resin was found to be 1.5 mmole MBT/MBI anion per gram of dry resin. Similarly, the exchange capacity of the 2-butylthiobenzimidazole, 2-allylthiobenzimidazole and 2-benzylthiobenzimidazole anion supported resin each was found to be 1 mmole per gram of dry resin.

General Procedure for the Synthesis of S-Alkyl and S-Acyl Derivatives of MBT/MBI.- A mixture of MBT/MBI anion supported resin (10 g, 15 mmoles) and alkyl halide or acid chloride (15 mmoles) in acetone (25 mL) was stirred for (30-45 min or 5-15 min) depending on the reactivity of the alkyl halide or acid chloride, respectively. The progress of the reaction was monitored by TLC (MBT; pet. ether:chloroform, 8:2 and MBI; chloroform:acetone, 9:1). The resin was then filtered off and washed with acetone (3 x 5 mL). The filtrate was dried over anhydrous sodium sulfate, followed by removal of the solvent to afford the products listed in *Tables 1 & 2.*

Dimeric Derivatives.- The dimer-type products, namely, dithioethers and dithioesters, were synthesized by the same procedure using α,ω-dibromoalkanes and diacyl chlorides instead of alkyl halide and acid chloride, respectively with the mole proportions of supported resin and α,ω-dibromoalkane or diacyl chloride as 1:0.5. The formation of dithioesters was more rapid (5-15 min) than that of dithioethers (60 min).

Furthermore, S-alkylated products were supported on the resin using aqueous KOH and then treated with alkyl halides to give S,N-dialkylated products (25-45 min; TLC, chloroform:acetone, 8:2). Again α,ω-*bis*-2-benzimidazoylthioalkanes were synthesized by reaction of a mixture of MBI anion supported resin (20 g, 30 mmoles) and α,ω-dibromoalkanes (15 mmoles) in acetone (40 mL) by the above procedure. These products were purified further by recrystallization from 95% ethanol to give colorless needles.

Table 1. MBT Derivatives

Cmpd	Yield (%)	mp (bp/mm) (°C)	*lit.* mp (bp/mm) (°C)	^{1}H NMR (δ)
1a	96	48	48-49[17,22]	----
1b	95	26	26[4,17]	----
1c	93	(172/15)	(168-175/15)[18]	----
1d	90	(110-112/0.5)	(110-115/0.5)[16,18]	----
1e[b]	91	240-242	----	2.65 (m, 2H, middle CH_2); 3.70 (t, 2H, CH_2); 4.74 (t, 2H, CH_2Br); 7.67-8.30 (t, t, d, d (m), 4H, Ar-H)
1f	92	(145-146/1)	(145-146/1)[18]	----
1g	89	(127-129/0.5)	(125-128/0.5)[18]	----
1h	88	(139-140/0.5)	(139-140/0.5)[18]	----
1i	94	(126-128/0.05)	(126-128/0.05)[16]	----
1j	95	40	39-40[22]	----
1k	95	178-179	178-181[4]	----
1l[a]	98	130	129-131[4]	7.41-8.05 (m, 4H & 5H, Ar-H)
1m	96	166-167	165-167[22]	----
1n	92	142	141-142[22]	----
1o[a]	96	66	66-67[4]	1.42 (t, 3H, CH_3); 4.41 (q, 2H, CH_2); 7.42-8.10 (m, 4H, Ar-H);
1p[a]	95	89	89-90[4]	5.51 (s, 2H, CH_2); 7.32-8.10 (m, 4H & 5H, Ar-H)
2a[a]	93	139-140	----	3.82 (s, 4H, SCH_2CH_2S); 7.21-7.85 (t, t, d, d (m), 8H, Ar-H)
2b[a]	92	210	----	1.12 (m, 2H, middle CH_2); 3.72 (t, 4H, $2SCH_2$); 7.18-7.75 (t, t, d, d (m), 8H, Ar-H)
2c[a]	95	135	----	7.20-7.54 (m, 8H, Ar-H)
2d[a]	94	164-165	164-165[22]	4.80 (s, 2H, $COCH_2CO$); 7.22-7.42 (m, 8H, Ar-H)
2e[a]	94	145	----	2.80 (t, 4H, 2 $COCH_2$); 7.26-7.40 (m, 8H, Ar-H)
2f[a]	96	120	119-121[22]	1.15 (m, 4H, middle CH_2CH_2); 2.42 (t, 4H, $2COCH_2$), 7.23-7.48 (m, 8H, Ar-H)

a) In $CDCl_3$ **b**) In $CDCl_3$ + DMSO-d_6

Table 2. MBI Derivatives

Cmpd	Yield (%)	(°C) mp	*lit.* (°C)	^{1}H NMR[a] (δ)
3a	94	203	203-205[22]	----
3b[b]	94	170	170-170.5[22]	1.40 (t, 3H, CH_3); 3.29 (q, 2H, CH_2); 7.23 & 7.60 (each m, each 2H, Ar-H)
3c	92	152	153[22]	----
3d[c]	90	115	----	2.67 (m, 2H, middle CH_2); 3.70 (t, 2H, S-CH_2); 4.45 (t, 2H, CH_2Br); 7.25 -7.72 (m, 4H, Ar-H)
3e	90	135	134-135[15]	----
3f	89	140-142	140-142[19]	----
3g	95	184	184-185[19]	----
3h	88	214	214-215[22]	----
3i	96	143-145	143-145[22]	----
3j[b]	97	265	----	6.96-7.21 (m, 9H, Ar-H)
4a[d]	94	238	238-239[15]	3.48 (s, 4H, CH_2CH_2S); 7.25 (m, 8H, Ar-H)
4b[d]	92	210	----	1.65 (m, 2H, middle CH_2); 3.38 (t, 4H, 2 SCH_2); 7.20 (m, 8H, Ar-H)
4c[d]	91	218	218-220[19]	1.72 (m, 4H, 2 CH_2); 3.14 (m, 4H, 2 SCH_2); 7.28 (m, 8H, Ar-H)
5a[a]	88	122	----	0.90 (t, 6H, 2 CH_3); 1.14-2.05 [m, 8H, 2(CH_2CH_2)$_2$]; 3.40 (t, 2H, SCH_2); 4.05 (t, 2H, NCH_2); 7.15-7.65 (m, 4H, Ar-H)
5b[a]	90	165	----	4.04 (d, 2H, SCH_2); 4.71 (d, 2H, NCH_2); 4.90-5.12 (dd, 2H, =CH_2); 5.32-5.43 (dd, 2H, = CH_2); 5.85 (m, 1H, CH); 6.05 (m, 1H, -CH=); 7.11-7.73 (m, 4H, Ar-H)
5c[d]	92	116	116-117[19]	4.35 (s, 2H, SCH_2); 5.12 (s, 2H, NCH_2); 7.17 (m, 10H, Ar-H); 7.40 (m, 4H, Ar-H)

a) In $CDCl_3$; b) In $CDCl_3$ + DMSO-d_6; c) In $CDCl_3$ + TFA; d) In TFA

Table 3. Combustion Analysis Data of Compounds **1-5**

Cmpd	Elemental Analysis Data (Found)			
	C	H	N	S
1a	53.00 (53.12)	3.89 (3.83)	7.72 (7.78)	35.38 (35.36)
1b	55.35 (55.28)	4.64 (4.67)	7.17 (7.14)	32.84 (32.90)
1c	57.38 (57.46)	5.30 (5.33)	6.69 (6.65)	30.64 (30.62)
1d	57.38 (57.48)	5.30 (5.30)	6.69 (6.65)	30.64 (30.64)
1e	41.67 (41.55)	3.50 (3.48)	4.86 (5.05)	22.25 (22.35)
1f	59.15 (59.08)	5.87 (5.92)	6.27 (6.25)	28.71 (28.72)
1g	60.72 (60.82)	6.37 (6.32)	5.90 (5.94)	27.02 (26.97)
1h	60.72 (60.80)	6.37 (6.35)	5.90 (5.98)	27.02 (26.99)
1i	57.93 (57.85)	4.38 (4.43)	6.76 (6.75)	30.93 (30.98)
1j	65.33 (65.41)	4.31 (4.26)	5.44 (5.47)	24.92 (24.94)
1k	51.65 (51.58)	3.37 (3.46)	6.69 (6.75)	30.64 (30.59)
1l	61.97 (62.10)	3.34 (3.36)	5.16 (5.14)	23.63 (23.60)
1m	63.13 (62.98)	3.89 (3.94)	4.91 (4.97)	22.47 (22.48)
1n	64.62 (64.66)	3.73 (3.75)	4.71 4.67)	21.56 (21.59)
1o	50.19 (50.17)	3.79 (3.82)	5.85 (5.88)	26.80 (26.75)
1p	59.78 (59.84)	3.68 (3.64)	4.67 (4.72)	21.28 (21.31)
2a	53.30 (53.35)	3.35 (3.34)	7.77 (7.75)	35.57 (35.56)
2b	54.51 (54.62)	3.77 (3.78)	7.48 (7.32)	34.24 (34.22)
2c	49.46 (49.45)	2.08 (2.12)	7.21 (7.28)	33.01 (32.90)
2d	50.72 (50.74)	2.50 (2.46)	6.96 (6.98)	31.86 (31.89)
2e	51.90 (51.92)	2.90 (3.00)	6.72 (6.67)	30.79 (30.80)
2f	54.03 (53.95)	3.63 (3.66)	6.30 (6.26)	28.85 (28.92)
3a	58.51 (58.46)	4.91 (4.97)	17.06 (16.96)	19.52 (19.58)
3b	60.64 (60.68)	5.65 (5.64)	15.72 (15.68)	17.99 (18.03)
3c	62.46 (62.54)	6.29 (6.30)	14.57 (14.54)	16.68 (16.66)
3d	44.29 (44.32)	4.09 (4.07)	10.33 (10.28)	11.82 (11.83)
3e	64.04 (64.12)	6.84 (6.78)	13.58 (13.60)	15.54 (15.56)
3f	63.13 (63.02)	5.30 (5.38)	14.72 (14.74)	16.96 (16.94)
3g	69.97 (69.88)	5.03 (5.14)	11.66 (11.68)	13.34 (13.30)
3h	51.91 (51.87)	3.87 (3.88)	13.45 (13.46)	15.40 (15.38)
3i	56.23 (56.12)	4.19 (4.24)	14.57 (14.58)	16.68 (16.64)
3j	66.12 (66.08)	3.96 (3.98)	11.02 (11.18)	12.61 (12.78)
4a	58.87 (58.58)	4.32 (4.42)	17.16 (16.98)	19.64 (19.83)
4b	59.97 (59.82)	4.74 (4.76)	16.45 (16.68)	18.84 (18.96)
4c	60.99 (61.19)	5.12 (5.11)	15.80 (15.70)	18.09 (18.05)
5a	68.65 (68.68)	8.45 (8.32)	10.67 (10.72)	12.22 (12.20)
5b	67.79 (67.86)	6.13 (6.14)	12.16 (12.02)	13.92 (13.80)
5c	76.33 (76.22)	5.49 (5.56)	8.48 (8.52)	9.70 (9.72)

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† This work on MBT was presented at 21st Annual National Conference of Indian Council of Chemists, Jabalpur, 2002, Abstract OP-40, p. 103 and the work on MBI was presented at National symposium on Frontiers in Organic Chemistry, Kolhapur, 2002, Abstract P-45, p. 68.

†† This paper is dedicated to Prof. R. B. Mane, Department of Chemistry, Shivaji University, Kolhapur 416 004 (M. S.) INDIA.

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AN EFFICIENT SYNTHESIS OF TRICYCLIC COMPOUNDS, (±)-(4aβ,8aβ,10aα)-1,2,3,4,4a,6,7,8,8a,9,10,10a-DODECAHYDRO-1,1,4a-TRIMETHYL-2-OXOPHENANTHRENE-8a-CARBOXYLIC ACID, ITS METHYL ESTER, AND (±)-(4aβ,8aβ,10aα)-3,4,4a,6,7,8,8a,9,10,10a-DECAHYDRO-8a-HYDROXYMETHYL-1,1,4a-TRIMETHYLPHENANTHREN-2(1*H*)-ONE

Submitted by (09/09/05)

Tadashi Honda*, Yukiko Honda, Hidenori Yoshizawa, and Gordon W. Gribble*

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Our ongoing efforts for the improvement of anti-inflammatory and anti-proliferative activity of oleanolic acid analogues led us to discover 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO, **1**) and related compounds.[1]