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Synthesis of Some Novel Bis Type 2-Mercapto Benzimidazole Derivatives

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ABSTRACT

The conventional methodology was adopted to synthesize the title compounds.The synthesis of titled compound from starting material i.e substituted 2-mercapto benzimidazoles was prepared from substituted o-phenylenediamine and carbon disulphide in presence of KOH in single step, initially the substituted 2-mercapto benzimidazole compounds are subjected to S-acylation by treating with acetyl chloride in acetone in the presence of potassium carbonate, results formation of acylated compounds. Which are further treated with 1,2-dibromo ethane and 1,3-dibromo propane using potassium carbonate as deacidifying agent, to get their respective substituted bis type 2-mercapto benzimidazole derivative.

Key words: Benzimidazole, 2-mercapto benzimidazole, O-PhenyleneDiamine.

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INTRODUCTION

A number of benzimidazole-2-thiones have been synthesized by the general method described by Van allan and Deacon [1]. 2-meracapto benzimidazole which contain a hydrogen atom attached to nitrogen in the 1-position readily tautamerised [2-3]. N-acetyl benzimidazole has been prepared by heating 2-benzimidazole carboxylic acid with acetic anhydride decarboxylation occurs and forms the product. The majority of data on benzimidazoline-2-thiones relates to S-alkylation and closely related processes are synthesis of 2-thiocynatobenzimidaozle form the reaction of benzimidazoline-2-thiones with cynogen chloride or bromide and 2-benzimidazolyl thiocarbamtes from addition of the 2-thiones to aryl isocynates [4-5]. Other routineprocedures are the oxidation of 2-thiones to bisbenzimidazolyldisulphide and benzimidazole 2-sulfonic acid by hydrogen peroxide. The reviews clearly emphasize the importance of hetrocyclic in the naturally occurring as well as antimicrobial,antiprotozoal,antimaerial,and antiallargicetc[6-11]. This point encouraged further investigation in the field. The logic supporting the work presented in this paper was formulated, bearing in the mind that thebiological activities of known moieties and attempting certain structural modification or adaption in the light of the recent trends in the drug research incorporating newly emerged pharmacophores on existing moiety. Hence in the study we plan synthesize some novel bis type 2-mercapto benzimidazole by treating with dibromo alkanes using potassium carbonate as deacidifying agent.

MATERIALS AND METHOD

Step-1[12]

1.Preparation of 2-mercapto benzimidazole.(compound-1).

A mixture of 10.8 gm (0.1 mole) of o-phenylenediamine 5.65 gm (0.1 mole) of potassium hydroxide and 7.67 gm (0.1 mole,6.19 ml) of carbon disulfide 100 ml of 95% ethanol and 15 ml of water in a 500 ml round bottom flask heated under reflux for 3 hours .then added 1-1.5 gm of charcoal cautiously and the mixture is further heated at the reflux for 10 minutes the charcoal is removed by filtration. The filtrate is heated to 60-70^{0}c , 100 ml of warm water is added ,and acidified with dilute acetic acid with good stirring . the product separated as glistening white crystals ,and the mixture is placed in a refrigerator for three hours to complete the crystallization. The product is collected on a buckner funnel and dried over night at 40^0 c. the dried product is recrystallised with etanol. The melting point is 300-305^{0}c , yield 8.5(73%), mol.wt.is 150 gm/mole.

2. Preparation of 5-methoxy 2-mercapto benzimidazole.(compound-2).

15.2 gm (yield 84) of 5 methoxy 2-mercapto benzimidazole was obtained from 13.8 gm (0.1 mole) of 4 – methoxy o-phenylene diamine,5.65gm (0.1 mole) of potassium hydroxide and 7.67 gm (0.1 mole,6.19 ml) of carbon di sulfide in the same manner as in (1). Melting point 258-262^0 c mol.wt.is 180 gm/mole.

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3. Preparation of 5-difloromethoxy 2-mercapto benzimidazole.(compound-3).

17gm(78%) of 5-difloromethoxy 2-mercapto benzimidazole was obtained from 17.4 gm (0.1 mole) of 4-difloro methoxy o-phenylenediamine, 5.65 gm (0.1 mole) of potassium hydroxide and 7.67 gm (0.1 mole 6.19 ml) of carbon di sulfide in the same manner as in (1). Melting point 255-256^0 c, mol.wt.is 216 gm/mole.

Step 2

1.Preparation of S-(1H-benzimidazole-2-yl) ethanethiote. (compound-IV).

10mg(0.06mole) of 2- mercaptobenzimidazole, 8.2gm (0.06mole) of potassium carbonate is taken in a 250ml RBF to this add 120ml of acetone and stir the mixture on magnetic stirrer for 10min then add 4.7gm (0.06) of acetylchloride by dropwise using droping funnel. After complete addition, reflux the reaction mixture for about 4 hrs. cool the reaction mixture and add 100ml of water, filter and wash with water. Practical yield is 9.6gm (75%) melting point is 253-255^0 C, mol. Wt. is 192gm/mole.

2. Preparation of S-(5-methoxy 1H-benzimidazol-2-yl)ethanethiote.(compound-V).

11.3gm of S-(5-methoxy 1H-benzimidazol-2-yl) ethanethiote is obtained from the 10.8gm(0.06mole) of 5-methoxy 2-mercapto benzimidazole, 8.2gm (0.06mole) of potassium carbonate and 4.7gm (0.06) of acetylchloride as in the same manner in (1).Practical yield is 11.3gm(84%). Melting point is 232-234^0 C, mol.wt. is 222gm/mol.

3.Preparation of S-(5difloro-methoxy 1H-benzimidazole-2-yl)etanethioate. (compound-VI).

12.4gm of S-(5difloro-methoxy 1H-benzimidazole-2-yl)etanethioate is obtained from the 13gm (0.06mole) of 5-methoxy 2-mercapto benzimidazole, 8.2gm(0.06mole) of potassium carbonate and 4.7gm (0.06) of as in the same manner in (1). Practcal yield is 15gm(82%). Melting point is 218-221^0 C, mol. Wt. is 258gm/mole.

Step-3[13,14]

1. Syntesis of S,S'-[ethane-1,2-diylbis(1H-benzimidazole-1,2-diyl) diethanethioate (compound-a).

5gm (o.026mole) of compound-IV and 2.3gm(0.013mole) of 1,2dibromoetane were dissolved in 60ml of etanol, and 5gm of potassium carbonate is added as a deacidifying agent. And thus obtained solution was refluxed under stirring on water bath for about 14 hrs. After cooling, it was neutralized with 2N aqeousNaOH solution. Crystals thus formed were collected by filtration. And then washed with hydrous etanol and acetonitrile. Yield is 8.4gm (79%), Melting point is 226-228^0 C, Mol.Wt.is 410.5gm/mole.IR (KBr): NH (str): 3386 Ar-CH (str):

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3023,3052,C-N(str):1270,1293,1346,1441C=C(str):1467,1592C-S(str):617,695 C-H methylene(str):2866, C=O(str):1715,1750,1800. EI ms:m/z: 411(M+1), 433.

2.Preparation of S,S'-[propane-1,2-diylbis(1H-benzimidazole-1,2-diyl)] diethanethioate.(compound-b).

10.1 gm (yield 91%) of the intended compound was obtained from 5 gm (0.026 mole) of compound -4) and 2.6 gm (0.013 mole) of 1,3 – dibromopropane in the same manner as in (1). Melting point is 197-199^0 c mol.wt.is 424.5 gm/mole. IR(KBR):NH(str):3382,Ar-CH(str):3061,3133, C-N(str):1272,1298,1352, C=C(str):1436,1470,1503,1591,CS(str):617,667,C H methylene(str):2880,C=O(str):1730,1780.

3. Preparation of S,S'-[ethane-1,2-diylbis (5-methoxy 1H-benzimidazole-1,2-diyl)]diethanethioate.(compound-c).

8.9 gm (yield 85%) of the intended compound was obtained from 5 gm (0.02 mole) of compound-5 and 2.0 gm (0.011 mole) of 1,2 dibromoethane in the same manner as in (1).melting point is 188-190^0 C ,mol.wt.is 470.5gm/mole. IR(KBr):NH(str):3304,Ar-CH(str):3004,3025,3061,C-N(str):1267,1294,1343,C=C(str):1433,1460,1499,1596,C-S(str):627,675,C-Hmethylene(str):2886,C-H methyl:2954,C=O:1750,1790.

4. Preparation of S,S'-[propane-1,2-diylbis (5-methoxy 1H-benzimidazole-1,2-diyl)]diethanethioate.(compound-d).

9.3 gm (yield 85%) of the intended compound was obtained from 5 gm (0.02 mole) of compound-5 and 2.2 gm (0.01 mole) of 1,3 dibromopropane in the same manner as in (1).melting point is 202-205^{0}C ,mol .wt.is 484.5 gm /mole. IR(KBr):NH(str):3348,Ar-CH(str):3068,C-N(str):1270,1301,1343,C=C(str):1449,1489,1595,C-S(str):624,C-Hmethylene (str):2831,2934,C-H methyl:2884,2982,C=O:1720,1780. EI ms:m/z:485.2(M+1),221,507.

5. Preparation of S,S'-[ethane-1,2-diylbis (5-difloromethoxy 1H-benzimidazole-1,2-diyl)]diethanethioate.(compound-e).

8.2gm (yield 78%) of intended compound was obtained from 5gm (0.019mole) of compound-VI and 1.74gm (0.009mole) of 1,2-dibromoetane in the same manner as in (1). Melting point is 227-229^{0}C, Mol.wt. is 542.5gm/mol.IR(KBr):NH (str):3548, Ar-CH(str):3098, C-N(str):1256, 1300, 1338, 1354, C=C(str):1471, 1498, 1527, 1557, C-S(str):615, 687, C-H methylene (str) : 2871, C-F : 1120, 1221, 1257, 1300, C=O : 1735, 1760, 1800.

6.Preparation of S,S'-[propane-1,2-diylbis(5-difloro methoxy 1H-benzimidazole-1,2-diyl)] diethanethioate. (compound-f).

8.8gm (yield 82%) of the intended compound was obtained from 5gm (0.019mole) of compound-VI and 1.8gm (0.009mole) of 1,3-dibromopropane in the same manner as in (1).

Melting point is 226-231^{0}C, Mol.wt. is 556.5gm/mole.IR(KBr):NH (str):3414, Ar-CH(str):3050, C-N(str):1269, 1297, 1347, C=C(str):1446, 1481, 1597, C-S(str):618, 641, 678, C-H methylene (str) : 2872, C-F : 1179, 1229, 1269, 1297, C=O : 1730, 1745, 1790.

Experimental

Melting points were determined by using precision melting point apparatus in open capillaries and are uncorrected .the purity of the compounds was checked by tlcon silica gel g plates using n- hexane ethyl acetate and methanol :chloroform solvent system and ultraviolet lamp and iodine chambers used as a visualizang agent. ir –spectra were recorded using kbr pellets on a Shemadzu8000 series spectro-photometer ^{1}h-nmr spectra on bruker 400 mh z spectrophotometer using ethanol as solvent and tms as internal standard (chemical shift values expressed in ppm).

Anti-bacterial Activity

The antibacterial activity was performed by cup-plate method. All the synthesized compounds were dissolved in 10 ml DMF at a concentration of 50 mcg/mL. The respective bacterial culture was spread (swabbed) into the nutrient agar plates for uniform distribution of colonies. Using a sterile cork borer, 8 mm wide well was made on each agar plates. All the synthesized compounds (50 mcg/mL) were poured into each wells using a sterile micropipette and Ampicillin (50 mcg/mL) were used as standard. The plates were incubated for 24 hr at 37^{0}C. After incubation, the zone of inhibition was measured.

Antifungal Activity

The antifungal activity was tested against *Candida albicans*by cup plate method. All the synthesized compounds were dissolved in DMF solution at a concentration of250 mcg/mL. The fungal culture was spread (swabbed) into the sabouraud dextrose agar plates for uniform distribution of colonies. Using a sterile cork borer, 8 mm wide well was made on each agar plates. All the synthesized compounds (250 mcg/mL) were poured into each wells using a sterile micropipette and Ketoconazole (250 mcg/mL) were used as standard. The plates were incubated for 48 h at 27^{0}C. After incubation, the zone of inhibition was measured.

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Scheme:

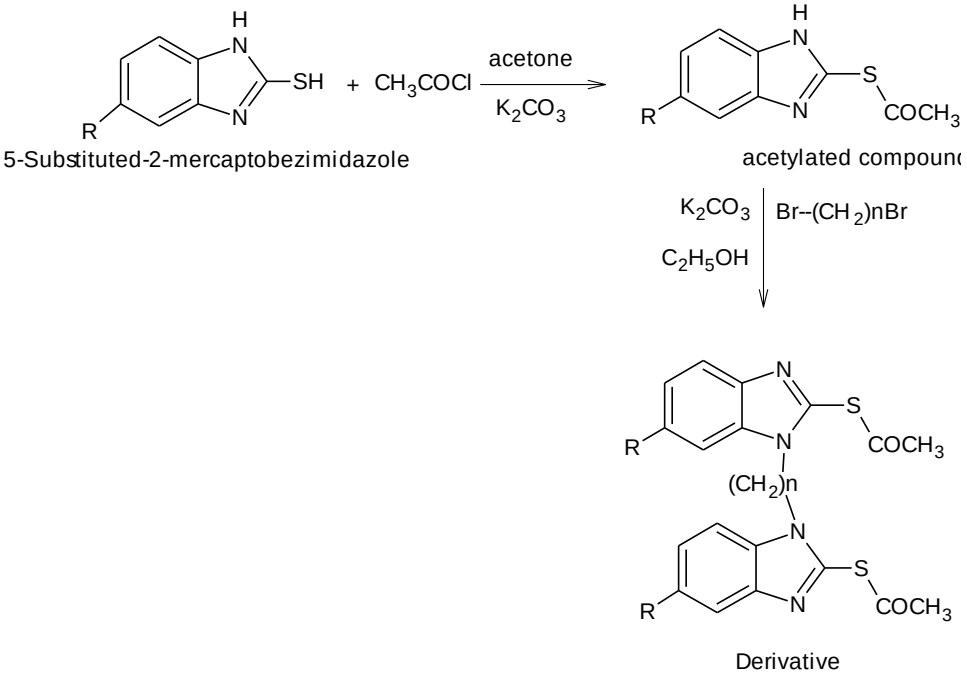

Table No1: List of Different Derivatives Used.

Compound	R	n
2a	H	2
2b	H	3
2c	OCH_3	2
2d	OCH_3	3
2e	$OCHF_2$	2
2f	$OCHF_2$	3

Anti- bacterial activities of benzimidazole derivatives

Table No 2: Antibacterial Activity of Benzimidazole Derivatives.

Sl No	Compound	Conc. mcg/ml	E.Coli	S.Aureus.
1	2a	50	7	8
2	2b	50	8	9
3	2c	50	12	14
4	2d	50	11	12
5	2e	50	9	11
6	2f	50	10	11
7	Ampicillin	50	24	25
		100	25	25

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Anti-fungal activities of benzimidazole derivatives

Table no 3: Antifungal activity of benzimidazole derivatives

Sl No	Compound	Conc.mcg/ml	Candida albicans
1	2a	250	+
2	2b	250	+
3	2c	250	-
4	2d	250	-
5	2e	250	+
6	2f	250	+
7	Ketoconazole	250	-

Note : (-) No Growth, (+) growth.

RESULT AND DISCUSSION

A number of benzimidazole-2-thiones have been synthesized by the general method described by Van allan and Deacon [1]. The formation of new chemical analogues was indicted by the melting point and Rf value. The structure of the synthesized compounds was established by spectral (IR and 1H NMR) . The NH band (3340 – 3548 cm^{-1}) and NH proton signal (4.88 – 5.75 ppm) of 2-mercaptobenzimidazole in IR and 1H NMR spectrum respectively in all the synthesized compounds confirmed the reaction was not taken at 1Hposition. The presence of CHmethylene stretching (2880,2886,2832 cm^{-1}) and CH2 proton signal (3.70 – 5.78 ppm) in IR and 1H NMR spectrum respectively together with the absence of SH proton of 2-mercaptobenzimidazole confirmed the formation of the titled compounds. Among the compounds tested, all the compounds showed moderate antibacterial and antifungal activities at a concentration of 50 mcg/mL and 250 mcg/mL when compared to ampicillin and ketoconazole respectively (Table 2,3).

CONCLUSION

The present work deals with the preparation of some novel bis type 2-mercapto benzimidazole by treating with di-bromo alkanes using potassium carbonate as deacidifying agent. This method of synthesis is accurate and gives high percent purity with a greater yield. All the derivatives prepared by this method are analysed by Mass and IR.

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