Srikanth Gurrala. et al. / International Journal of Pharmacy & Therapeutics, 1(2), 2010, 92-97.

ISSN 0976 – 0342

International Journal of Pharmacy & Therapeutics

Journal homepage: www.ijptjournal.com

IJPT

SYNTHESIS OF SOME NOVEL BIS TYPE 2-MERCAPTO BENZIMIDAZOLE DERIVATIVES

***Srikanth Gurrala, J. Venkateshwar Rao, T. Manish Kumar, D. KumaraSwamy**

Department of Pharmaceutical Chemistry, B.L.D.E.A's College of Pharmacy
Bijapur, Karnataka, 586103.

ABSTRACT

The conventional methodology was adopted to synthesize the titled compounds. The synthesis of titled compounds from starting material i.e substituted 2-mercapto benzimidazoles was prepared from substituted o-phenylene diamine and carbon disulfide 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 in ethanol using potassium carbonate as deacidifying agent. To get their respective substituted bis type 2-mercapto benzimidazole derivatives.

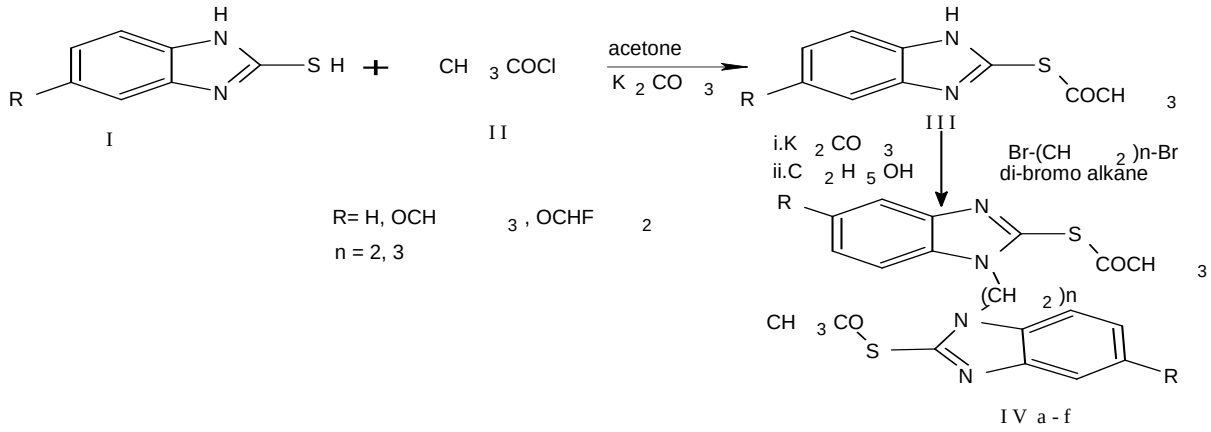
Keywords: Benzimidazole, Dibromo alkanes.

INTRODUCTION

A number of benzimidazoline 2-thiones have been synthesized by the general method described by Van allan and Deacon (Hollgens EL *et al*., 2010). 2-mercapto-benzimidazole which contain a hydrogen atom attached to nitrogen in the 1-position readily tautamerised (Martin VE *et al*., 1989, Wright JB *et al*., 1951). 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- thione relates to S-alkylation and closely related processes are the synthesis of 2-thiocyanatobenzimidazoles from the reaction of benzimidazoline 2-thione with cynogen chloride or bromide and 2-benzimidazolyl thiocarbamates from addition of the 2-thione to aryl isocyanates (Day AR *et al*., 1950, Preston PN *et al*., 1974). Other routine procedures are the oxidation of 2-thiones to bis benzimidazolyl disulfides and benzimidazole 2-sulfonic acids by hydrogen peroxide. The reviews clearly emphasize the importance of Heterocycles in naturally occurring as well as synthetic agents and does an important class itself possess diversified pharmacological actions such as antimicrobial, antiprotozoal, antimalarial, and antiallergic etc (Fromtling RA *et al*., 1987). This point encouraged further investigation in the field. The logic supporting the work presented in this dissertation was formulated, bearing in mind that the biological activities of known moieties and attempting certain structural modification or adaptation in light of the recent trends in drug research incorporating newly emerged pharmacophores on existing moiety. Hence in the present study we plan synthesize some novel bis type 2-mercapto benzimidazoles by treating with dibromo alkanes using potassium carbonate as deacidifying agent. The synthesis of titled compounds is showed in scheme-1.

*** Correspondance Author**

Srikanth Gurrala
Email: Steev.g99@gmail.com



Scheme-1: Synthesis of Bis type 2-mercaptobenzimidazole derivatives (a-f)

MATERIALS AND METHODS

Melting points were determined by using Precision melting point apparatus in open capillaries and are uncorrected. The purity of the compounds was checked by TLC on silica gel G plates using n-Hexane, ethyl acetate (6:4) and methanol: chloroform (1:9) solvent system and Ultraviolet lamp and iodine chambers used as a visualizing agent. IR-spectra were recorded using KBr pellets on a SHEMADZU 8000 series spectro-photometer. 1H-NMR spectra on BRUKER 400 MHz Spectrophotometer using Ethanol as solvent and TMS as internal standard (chemical shift values expressed in ppm).

EXPERIMENTAL

GENERAL PROCEDURE FOR SYNTHESIS OF COMPOUND-I

1. Preparation of 2-mercapto benzimidazole

A mixture of 10.8gm (0.1mole) of o-phenylenediamine, 5.65gm (0.1mole) of potassium hydroxide and 7.67 gm (0.1mole, 6.19ml) of carbon disulfide, 100ml of 95% ethanol and 15 ml of water in a 500ml round bottom flask heated under reflux for three 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 60-70oC, 100ml 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 40oc. The dried product is recrystallised with ethanol. (Wagner EC *et al*., 1943)

IR (KBr):NH(str): 3154,3116, Ar-CH(str): 2981C-N(str):1259,1357,C=C(str):1513,1467, C-S(str): 601,660.
EI ms: m/z: 151(M+1).

2. Preparation of 5-methoxy 2-mercapto benzimidazole

15.2gm (yield 84) of 5-methoxy 2-mercapto benzimidazole was obtained from 13.8gm (0.1mole) of 4-methoxy o-phenylene diamine, 5.65 gm (0.1mole) of potassium hydroxide and 7.67 gm (0.1mole, 6.19ml) of carbon disulfide in the same manner as in (1).

IR (KBr):NH(str): 3304,3466,Ar-CH(str): 3007,3023,3063,C-N(str):1265,1335,C=C(str): 1468,1499,C-S(str): 577,628,C-H of CH3 : 2886,2962.EI ms: m/z: 181(M+1).

3. Preparation of 5-difloromethoxy 2-mercapto benzimidazole

17gm (78%) of 5-difloromethoxy 2-mercapto benzimidazole was obtained from 17.4gm (0.1mole) of 4-difloromethoxy o-phenylene diamine, 5.65 gm (0.1mole) of potassium hydroxide and 7.67 gm (0.1mole, 6.19ml) of carbon disulfide in the same manner as in (1).

IR (KBr):NH(str): 3851,Ar-CH(str): 2970,3099,C-N(str):1258,1336,1355,C=C(str): 1472,1497,1527,C-S(str): 616,653,690,C-F of CF2 : 1121,1181,1258,1336.EI ms: m/z: 217(M+1).

The Physicochemical parameters of above 5-substituted 2-mercaptobenzimidazole compounds (I) were showed in table-1.

GENERAL PROCEDURE FOR SYNTHESIS OF COMPOUND-III

1.1 Preparation of *S*-(1*H*-benzimidazol-2-yl) ethanethioate

10gm (0.06mole) of 2-mercapto benzimidazole (I), 8.2gm (0.06mole) of potassium carbonate is taken in a 250ml RBF to this add 120 ml of acetone and stir the mixture on magnetic stirrer for 10min. then add 4.7 gm (0.06) of acetylchloride (II) by dropwise using droping funnel. After complete addition, reflux the reaction mixture for about 4hrs. cool the reaction mixture and add 100ml of water , filter and wash with water.

1.2 Preparation of *S*-(5-methoxy1*H*-benzimidazol-2-yl) ethanethioate

11.3gm of *S*-(5-methoxy1*H*-benzimidazol-2-yl) ethanethioate (III) is obtained from the 10.8gm (0.06mole) of 5-methoxy 2-mercapto benzimidazole (I), 8.2gm (0.06mole) of potassium carbonate and 4.7 gm (0.06) of acetylchloride (II) as in the same manner in (1).

1.3 Preparation of *S*-(5difloro-methoxy1*H*-benzimidazol-2-yl) ethanethioate

12.4gm of *S*-(5-difloromethoxy1*H*-benzimidazol-2-yl) ethanethioate (III) is obtained from the 13gm (0.06mole) of 5-difloro-methoxy 2-mercapto benzimidazole (I), 8.2gm (0.06mole) of potassium carbonate and 4.7 gm (0.06) of acetylchloride (II) as in the same manner in (1).

The Physicochemical parameters of above acetylated compounds (III) were showed in table-2.

GENERAL PROCEDURE FOR SYNTHESIS OF COMPOUND-IV

1.1 Synthesis of *S*, *S*'-[ethane-1,2-diylbis(1*H*-benzimidazole-1,2-diyl)] diethanethioate (compound-a)

5gm (0.026mole) of compound-III and 2.3gm (0.013mole) of 1,2 dibromoethane were dissolved in 60ml of ethanol, and 5gm of potassium carbonate is added as a deacidifying agent. And the thus-obtained solution was refluxed under stirring on water bath for about 14hrs. After cooling, it was neutralized with 2N aqeous NaOH solution. Crystals thus formed were collected by filtration. And then washed with hydrous ethanol and acetonitrile (Kozo A *et al*., 1999, Amico JD *et al*., 1965)

IR(KBr): (NH,str):3386 3023,3052,(C-N,str):1270,1293,1346,1441,(C=C,str):1467,1592 (C-S,str):617,695,(C-H methylene,str):2866,(C=O,str):1715,1750,1800. EI ms : m/z : 411 (M+1), 433. H¹NMR (CDCl3,200MHZ): 7.21-7.62(m,8H, aromatic), 2.4(s, 6H, methyl), 4.21(m,4H, methylene).

Elemental Analysis: C(56.53%), H(3.69%), N(14.65%), O(8.37%), S(16.77%).

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

10.1gm (yield 91%) of the intended compound (IV) was obtained from 5gm (0.026mole) of compound-III and 2.6gm (0.013mole) of 1,3-dibromopropane in the same manner as in (1).

IR(KBr):(NH,str):3382,(Ar:CH,str):3061,3133,(CN,str):1272,1298,1352,(C=C,str):1436,1470, 1503,1591,(C-S,str):617,661,(C-Hmethylene,str):2880,(C=O,str):1730,1780. EI ms: m/z: 425.5 (M+1). H¹NMR (CDCl3,200MHZ):6.94-7.42(m,8H, aromatic), 2.4(s, 6H, methyl), 2.25-3.73(m,6H, methylene).

Elemental Analysis: C(59.41%), H(4.75%), N(13.20%), O(7.54%), S(15.11%).

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

8.9gm (yield 85%) of the intended compound (IV) was obtained from 5gm (0.02mole) of compound-III and 2.0gm (0.011mole) of 1,2-dibromoethane in the same manner as in (1).

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-H methylene,str):2886,(C-H methyl,str) :2954, (C=O,str): 1750,1790. EI ms: m/z: 471.5 (M+1).H¹NMR (CDCl3,200MHZ):7.12-7.41(m,6H, aromatic), 2.4(s, 6H, methyl,-C(=O)S),3.87(s,6H,methyl, -O-),4.21(m,4H, methylene).

Elemental Analysis: C(54.28%), H(4.10%), N(12.66%), O(14.46%), S(14.49%).

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

9.3gm (yield 85%) of the intended compound (IV) was obtained from 5gm(0.02mole) of compound-III and 2.2gm(0.01mole) of 1,3-dibromopropane in the same manner as in (1).

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-Hmethyl:2884, 2982, C=O:1720,1780. EI ms: m/z: 485.2(M+1), 221, 507. EI ms: m/z: 485.5 (M+1).H¹NMR (CDCl3,200MHZ): 7.12-7.26(m,6H, aromatic), 2.4(s, 6H, methyl,-C(=O)S),3.87(s,6H,methyl, -O-),2.25-3.73 (m,6H, methylene).

Elemental Analysis: C(57.01%), H(4.99%), N(11.56%), O(13.21%), S(13.23%).

1.5 Preparation of *S*, *S*'-[ethane-1,2-diylbis(5-difloro methoxy1*H*-benzimidazole-1,2-diyl)] diethanethioate. (compound-e)

8.2gm (yield 78%) of the intended compound (IV) was obtained from 5gm (0.019mole) of compound-III and 1.74gm (0.009mole) of 1,2-dibromoethane in the same manner as in (1).

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, 651, 687, C-H methylene (str):2871, C-F:1120, 1221, 1257, 1300, C=O:1735,1760,1800. EI ms: m/z: 543.5 (M+1).H¹NMR (CDCl3,200MHZ):6.77-7.41 (m,6H, aromatic), 2.4(s, 6H, methyl,-C(=O)S),7.36(s,2H, -O-CHF2),4.21(m,4H, methylene).

Elemental Analysis: C(46.69%), H(2.74%), F(14.77%), N(10.89%), O(12.44%), S(12.47%).

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

8.8gm (yield 82%) of the intended compound (IV) was obtained from 5gm (0.019mole) of compound-III and 1.8gm (0.009mole) of 1,3-dibromopropane in the same manner as in (1). IR(KBr):NH(str):3414, Ar-CH(str):3050, C-N(str):1269, 641, 678, C-H methylene (str): 2872, C-F: 1297, 1347, C=C(str):1446, 1481, 1597, C-S (str): 618, 1179, 1229, 1269, 1297, C=O: 1730,1745,1790. EI ms: m/z: 557.5(M+1). H¹NMR (CDCl3,200MHZ):6.99-7.41 (m,6H, aromatic), 2.4(s, 6H, methyl,-C(=O)S),7.36(s,2H, -O-CHF2),2.1-4.2(m,6H, methylene).

Elemental Analysis: C(49.64%), H(3.62%),F(13.65%), N(10.07%), O(11.50%), S(11.52%).

The Physicochemical parameters of above Bis type 2-mercaptobenzimidazole compounds (IVa-f) were showed in table-3.

RESULTS AND DISCUSSION

Table 1: Physicochemical parameters of 5-Substituted 2-mercapto benzimidazole derivatives

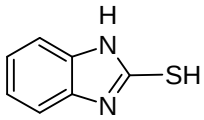
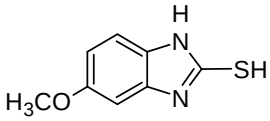
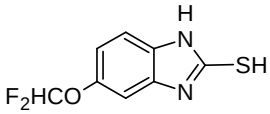
S.No	Compound (I)	Structure	Practical Yield (gm)	Yield(%)	Melting point(oC)
1	2-mercapto benzimidazole		8.5	73	300-305
2	5-methoxy 2-mercapto benzimidazole		15.2	84	258-262
3	5-difloro methoxy 2-mercapto benzimidazole		17	78	255-256

Table 2: The Physicochemical parameters of acetylated compounds (III)

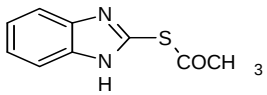
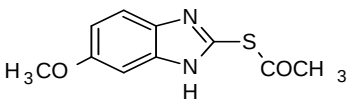
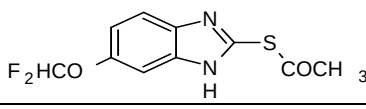
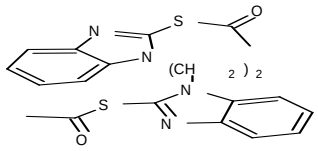
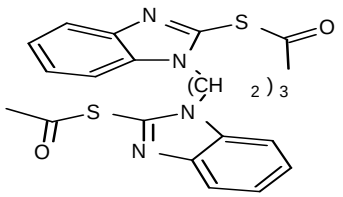
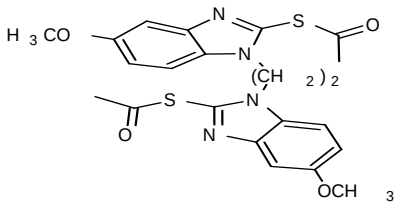
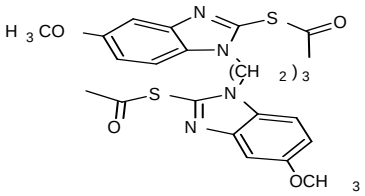
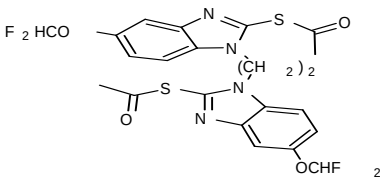
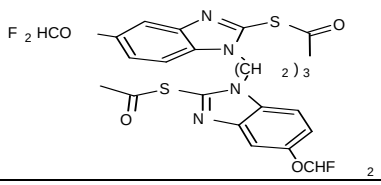
S.No	Compound (III)	Structure	Practical Yield (gm)	Yield(%)	Melting point (oC)
1	*S*-(1*H*-benzimidazol-2-yl) ethanethioate		9.6	75	253-255
2	*S*-(5-methoxy1*H*-benzimidazol-2-yl) ethanethioate		11.3	84	232-234
3	*S*-(5difloro-methoxy1*H*-benzimidazol-2-yl) ethanethioate		15	82	218-221

Table 3: The Physicochemical parameters of Bis type 2-mercaptobenzimidazole compounds (IVa-f)

S.NO	Compound code	Structure	Yield(%)	Melting point (0C)	Mol.wt gm/mole
1	a		79	232-2350C	410.5
2	b		91	197-1990C	424.5
3	c		84	188-1900C	470.5
4	d		85	202-2050C	484.5
5	e		78	227-2290C	542.5
6	f		82	226-2310C	556.5

CONCLUSION

The present work deals with the preparation of some novel bis type 2-mercapto benzimidazoles by treating with dibromo 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 analyzed by Mass, NMR and IR.

ACKNOWLEDGEMENT

I am very much thankful to Hetero Research Foundation, Hyderabad, for giving permission to carry out the analysis of synthesized derivatives by Mass, NMR and IR. I am very much thank full to Professor R.V. Heralagi B. L. D. E.A'S college of pharmacy, bijapur for his guidance, kind help and constant encouragement at every step during the progress of my work without which successful completion of this work would not have been possible. It is my pleasure to express my sincere thanks to Principal Dr. N.V.Kalyane of B.L.D.E.A'S college of pharmacy for providing laboratory facilities and chemicals.

I am also grateful to my scholars and my friends for their kind help from time to time at each and every step of my project work.

REFERENCES

Amico JD, Charlson W. Certain thiazolo [3,2-a] benzimidazoles and their production, United States Patent Office, 1965, 3, 225-59.

Day AR. Electronic mechanism of organic synthesis, 15, 2, American Book Company, USA, 1950, 242-243.

Fromtling RA, Recent Trends in the Discovery and Development and Evaluation of Antifungal Agents, Prous Barcelona, 12, 1987, 12-25.

Hollgens E L, Wagner EC. Some reactions of Nitriles as acid anammonides. *J.Org Chem*, 9(1), 1944, 31-49

Kozo A, Kazuhiro A. 2-mercaptobenzimidazole derivatives and antihyperlipemic agent or antiarteriosclerotic agent containing the same, United States Patent Office, 1999, 5962493.

Kubo K, Oda K, Kaneko T, Satho H, Nohara A. Synthesis of 2-[[4- fluroalkoxy -2-pyridyl] methyl] sulfinyl] -1H-benzimidazole as anti-ulcer agents. *Chem Pharma Bull*, 38, 1990, 2853-2858.

Martin VE, Kuffer A, Austel, Eds. Modern Drug Research, Paths to Better and Safer Drugs, Marcel Dekker, Inc, New York, 1989, 243-73.

Preston PN. Synthesis Reactions and Spectroscopic properties of benzimidazoles. *Chemical Reviews*, 74(3), 1974, 279-314.

Sung yun cho, Seung kyu kang, Sung soo kim, hyae gyeong cheon, Joong kwan choi, Eul kgun yum. Synthesis and SAR of benzimidazole derivatives containing oxycyclic and pyridine as a gastric H+-K+-ATPase inhibitors. *Bull Kor Chem Soc*, 22, 2001, 1217-1223.

Wagner EC and Millett WH. Synthesis of Benzimidazole, *Org Synt*, 2, 1943, 65.

Wright JB. The chemistry of benzimidazoles. *Chemical Reviews*, 48(3), 1951, 397-541.