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SYNTHESIS AND BIOLOGICAL ACTIVITIES OF 2-(α-*p* - SUBSTITUTED PHENYL-α-BENZIMIDAZOLO) METHYL BENZIMIDAZOLE

P. Jeyanthi[1,*], K. Sheela[1] and P.Pazhanisamy[2]
[1]Department of Chemistry, Bharathi Women's College, Chennai-600108, India.
[2]Department of Chemistry, Sir Theagaraya College, Chennai – 600021, India
*E-mail: jeyanthibwc@gmail.com

ABSTRACT
2-p-substituted phenyl-2-benzimidazolo acetonitriles (1a-3a) were prepared by the reaction of benzimidazole , p-substituted benzaldehydes and trimethylsillylcyanide in acetonitrile in the presence of bismuth tri chloride .A series of 2-(α-p -Substituted phenyl-α-benzimidazolo) methyl benzimidazoles (1b-3b) were synthesized by the reaction of 2-p-substituted phenyl-2-benzimidazolo acetonitrile(1a-3a) and o-phenylenediamine in presence of Conc. HCl. These compounds were characterized by IR , NMR and Mass spectroscopy. These compounds were exhibited both antibacterial and antifungal activities.
Keywords: Strecker reaction, benzimidazole, antifungal, antibacterial.

INTRODUCTION

Heterocycles form by far the largest of classical divisions of organic chemistry and are of immense importance biologically and industrially. The importance of imidazoline and benzimidazloes, units arises, because they are found in many biologically active compounds[1-5]. In addition, the benzimidazole moiety is found in various synthetic pharmaceuticals displaying a broad spectrum of biological activity including anti-ulcer, anti-tumor and anti-viral effects[6-9].

The addition of cyanide to imines (the Strecker reaction) [10] provides one of the most efficient methods for the synthesis of α-aminonitriles. α-Aminonitriles are important intermediates for the synthesis of amino acids[11] and various nitrogen containing heterocycles such as thiadiazoles and imidazoles[12] .The classical Strecker reaction is generally carried out with alkaline cyanides in aqueous solution. Among various cyanide ion sources,[13] trimethylsilyl cyanide is a safer and easily handled reagent compared to hydrogen cyanide, sodium cyanide, or potassium cyanide.

Recently, there has been considerable interest growing in the use of bismuth(III) halides as potential Lewis acids in various organic reactions[14] because they are inexpensive, relatively non-toxic, fairly insensitive to small amounts of water, and environmentally benign reagents. In this communication, we wish to report a simple and efficient method for the synthesis of a aminonitriles in the presence of a catalytic amount of bismuth(III) chloride in acetonitrile at room temperature.

Almost all benzimidazole derivatives with their two ring systems bear different functional substituents and this leads to essential modification of the physico-chemical, metabolic and pharmacokinetic properties of these drugs. Tissue selectivity of this type of antiulcer drugs is based on both their pH dependent accumulation, as weak bases in the acidic compartment of secreting parietal cell, and the subsequent acid-induced rearrangement of the parent compound to the pharmacologically active principle [15] .The present study deals with synthesis and biological activities of 2-(α-p -Substituted phenyl-α-benzimidazolo) methyl benzimidazoles.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. IR spectra (K Br) were recorded on a Perkin Elmer 1800(FTIR) spectrometer. PMR spectra (DMSO-d_6) on a Varian EM-390

spectrometer using TMS as an internal standard (chemical shift in δ ppm). Mass spectra were recorded on a Jeol JMS-D 300 Mass spectrometer operating at 70 eV. The purity of the compounds was confirmed by TLC using silica gel G. For TLC, Merck silica gel 60 G plate was used.

Antimicrobial Activity

The synthesized compounds in the present investigation have been tested for antimicrobial activity by well diffusion method. The organisms selected for the antifungal activity was carried out by using *Aspergillus flavus , Candida albicans and Cryptococcus*. The organisms selected for the antibacterial activity was carried out by using *Escherichia coli* , *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. The plates are prepared as per the standard methods[16].

Antimicrobial assay

Antibacterial analysis was followed using standard agar well diffusion method to study the antibacterial activity of compounds .Each bacterial and fungal isolate was suspended in Brain Heart Infusion (BHI) broth and diluted to approximately 10^5 colony forming unit (CFU) per mL. They were flood-inoculated onto the surface of BHI agar and then dried. Five-millimeter diameter wells were cut from the agar using a sterile cork-borer and 30 µL (5µg compound in 500 µL DMSO) of the sample solution were poured into the wells. The plates were incubated for 18 h at 37°C for bacteria and at room temperature for fungi. Antimicrobial activity was evaluated by measuring the zone of inhibition in mm against the test microorganisms. DMSO was used as solvent control. Chloramphenicol was used as reference antibacterial agent. Ketoconazole was used as reference antifungal agent. The tests were carried out in triplicates.

Synthesis of of 2-p-Hydroxyphenyl-2-benzimidazoloacetonitrile (1a)

A mixture of 0.005mol p-Hydroxybenzaldehyde , 0.005mol benzimidazole and 0.0075mol trimethylsilylcyanide in 10 ml acetonitrile in the presence of 0.0005mol bismuth tri chloride was stirred at room temperature for 12hrs. After completion of the reaction, the reaction mixture was partitioned between 10 ml of ether and 50ml of water. The organic layer was washed with 50 ml brine, dried over sodium sulphate and concentrated.The crude was recrystallized from benzene-petroleum ether mixture. The pure compound melted at 192-193 ^{0}C.

Synthesis of 2-p-Methylphenyl-2-benzimidazoloacetonitrile (2a)

The 2-p-methylphenyl-2-benzimidazoloacetonitrile (2a) was prepared by the reaction of p-methylbenzaldehyde and benzimidazole as described above. The crude was recrystallized from chloroform-petroleum ether mixture .The pure sample melted at 158-159 ^{0}C.

Synthesis of 2--p-Anisyl-2-benzimidazoloacetonitrile (3a)

2-p-Anisyl-2-benzimidazoloacetonitrile (5a) was synthesized by using p-Anisaldehyde. The crude was recrystallized from benzene and the pure compound melted at 163-164 ^{0}C.

Synthesis of 2-(α-p- Hydroxyphenyl -α -benzimidazolo) methyl benzimidazole (1b)

A mixture of 2-p-hydroxyphenyl-2-benzimidazoloacetonitrile (0.02mol) and o-phenylenediamine(0.02mol) 10L of concentrated hydrochloric acid was added .The mixture was heated for about 10 hours in an oil bath, maintained at a temperature of 150 ^{0}C. The product obtained was cooled for 4 h and the precipitated hydrochloride was filtered. It was washed with ethanol- ether mixture (1:5) and the product was transferred to a beaker. The hydrochloride was suspended in acetone and made alkaline with strong ammonia solution . It was diluted with water and the solid was filtered, washed with water, dried and recrystallized from chloroform. The pure sample melted at155-156 ^{0}C.

Infra Red Spectral Data (KBr), λ values in cm $^{-1}$

3452 (m) 3198 (w) 3110 (w) 2924 (s) 2854 (s) 2798 (m) 2666(w) 2500 (w) 2000 (w) 1820(w) 1743 (m) 1620 (m) 1500 (w) 1458 (s) 1405 (s) 1247 (m) 1208 (m) 1120 (m) 1021 (s) 845 (m) 751 (s) 670 (m) 589 (m) 543 (m) 460 (s)

Proton Magnetic Resonance Spectral Data ($CDCl_3$ / TMS), δ in ppm

4.6	(S)	1H	C-H methine
6.7 -7.3	(m)	12H	Aromatic protons
7.8	(S)	1H	- O-H phenolic

8.1 (S) 1H C –H benzimidazole

Mass Spectral Values ; m/z and %

341 (5) 340 (40) 322 (26) 250 (60) 247 (15) 223 (32) 222(18) 205 (25) 204 (35) 157 (55) 133 (45) 132 (30) 118 (38) 117 (100) 93 (53) 90(45) 63 (20)

Synthesis of 2-(α-p-Methylphenyl-α-benzimidazolo) methyl benzimidazole (2b)

A mixture of 2-p-Methylphenyl-2-benzimidazoloacetonitrile (2a) (0.02mol) and o-phenylenediamine (0.02mol) was taken in a 100 mL round bottom flask. About 5mL of concentrated hydrochloric acid was added .The contents were heated for 10 h in an oil bath maintained at 150-160^{0}C. The reaction mixture was kept overnight. The precipitated hydrochloride was filtered and washed with ethanol ether mixture (1:5). The resulting hydrochloride was suspended in acetone and was made alkaline by adding 30 mL of strong ammonia solution .The base was liberated by diluting it with water .The benzimidazole was filtered, washed with excess of water and dried. It was recrystallised from methanol . The pure sample melted at 166-167 ^{0}C.

Infra Red Spectral Data (KBr), λ values in cm $^{-1}$

3482 (m) 3409(w) 3313(w) 3145 (m) 3116(s) 2983 (m) 2926 (m) 2853 (m) 2767 (s) 2566(w) 2366(m) 2050 (s) 1850 (m)1740 (w) 1626 (s) 1530 (m) 1500(s) 1455 (w) 1402 (s) 1318 (w) 1230 (m) 1200(w) 1153(w) 1113 (w) 1072 (w) 1022 (s) 926 (m) 838 (m) 749(s) 671 (w) 609 (m) 556 (w) 449(s)

Proton Magnetic Resonance Spectral Data ($CDCl_3$ / TMS), δ values in ppm

4.6 (S) 1H C-H methane
7.1-7.3 (m) 13H Aromatic proton
8.1 (S) 1H C –H benzimidazole

Mass Spectral Values ; m/z and %

338 (8) 324 (30) 311 (42) 297 (20) 247 (15) 246(20) 234 (35) 221(8) 207(40) 206 (18) 205 (40) 157 (15) 130 (60) 118 (100) 117 (35) 116 (20) 90 (65) 77 (45) 63 (22)

Synthesis of 2-(α-p Anisyl-α – benzimidazolo) methyl benzimidazole (3b)

A mixture of 2-p-Anisyl-2-benzimidazoloacetonitrile (3a) (0.02mol) and o-phenylenediamine(0.02mol) was taken in a 100ml.round bottomed flask. About 5mL of concentrated hydrochloric acid was added and heated for 10 h in an oil bath maintaining the temperature at 160-165^{0}C. The reaction mixture was cooled and the precipitated hydrochloride was filtered .It was washed with ethanol ether mixture (1:5). and transferred to a beaker. Addition of excess of water liberated the base. The resulting solid was filtered, and washed with water and dried. It was recrystallized .from benzene. The pure sample melted at 188-189 ^{0}C.

Infra Red Spectral Data (KBr), λ values in cm $^{-1}$

3455 (m) 3366 (m) 3141 (m) 3026(w) 2959 (w) 2863 (w) 2805 (w) 2690 (m) 2598 (s) 2430 (m) 2366(m) 2043 (m) 1918 (w) 1774 (w) 1683 (w) 1625(m) 1531 (m) 1501(w) 1465 (w) 1402 (s) 1273 (m) 1236 (m) 1148 (m) 1025 (m) 930 (w) 878 (w) 837(m) 748 (s) 606 (m) 442(m)

Proton Magnetic Resonance Spectral Data ($CDCl_3$ / TMS), δ in ppm

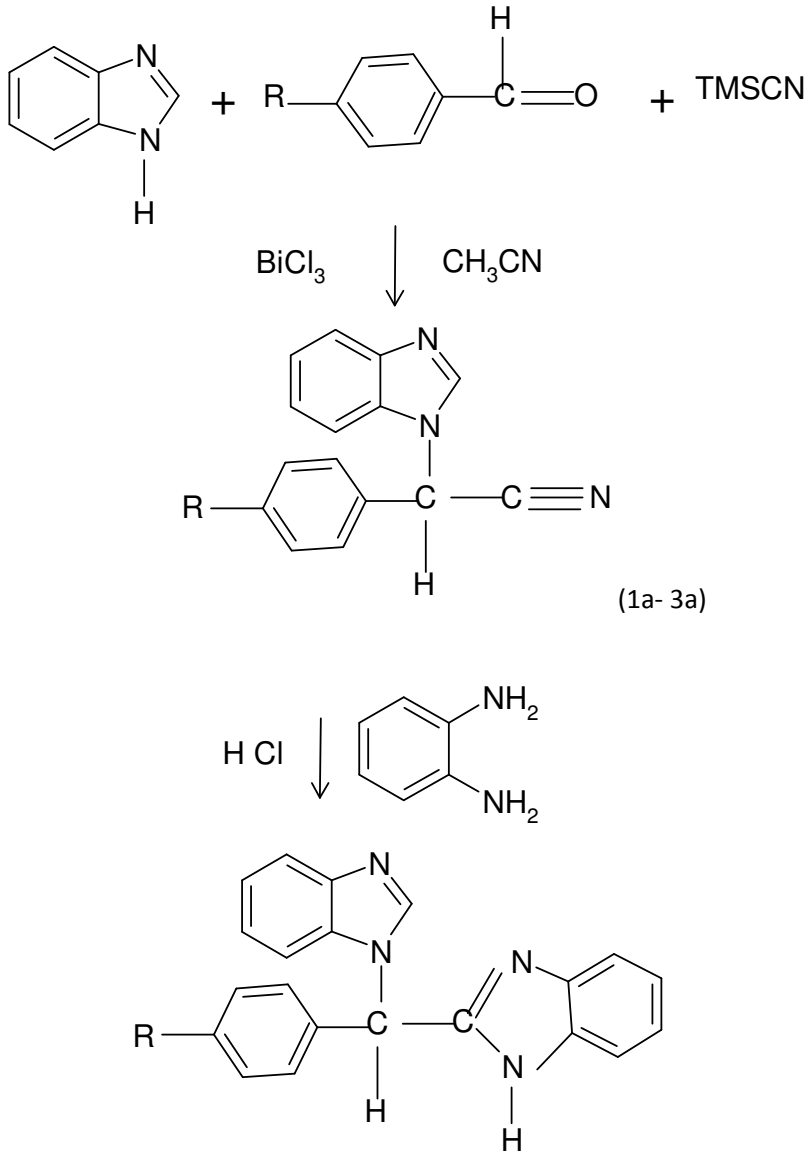
3.9 (S) 3H - CH_3 anisyl
4.6 (S) 1 H C-H methine
6.8 -7.4 (m) 12 H Aromatic protons
8.2 (S) 1H C –H benzimidazole

Mass Spectral Values ; m/z and %

355 (8) 354 (42) 347(16) 323 (45) 297(6) 284 (58) 264 (20) 237 (20) 236(6) 224(18) 210 (15) 205 (30) 195(65) 182 (12) 157 (50) 147 (25) 146(42) 130 (35) 118 (25) 117 (40) 107(100) 90(36) 63 (10)

RESULTS AND DISCUSSION

Series of 2-(α-p -Substituted phenyl-α-benzimidazolo) methyl benzimidazoles (1b-3b) were synthesized by the reaction of 2-p-substituted phenyl-2-benzimidazolo acetonitrile(1a-3a) and o-phenylenediamine in presence of Conc. HC. The synthetic route of these compounds were represented as Scheme-1.



(1b-3b); R = OH , CH_3, OCH_3

Scheme-1

Biological activities

The antibacterial screening of 1b, 2b and 3b compounds inhibited the activity of the following bacteria Escherichia coli, Pseudomonas aeruginosa and Staphylococcus Aureus(Table 1). Thus, compound **2b** showed a higher activity against all the screened bacteria .This activity was more pronounced against Gram-negative than Gram-positive bacteria. This could be as a result of the morphological differences between these micro-organisms. The antifungal screening of 1b, 2b and 3b

compounds for the following fungi : Aspergillus niger, Candida albicans and Candida tropicalis(Table 1). The compound 2b only showed activities against for all fungi and the compound 3b showed some activity against Candida albicans. The compound 1b inactive against all the fungi. Some selected photographs were shown.

Table-1: Antibacterial and Antifungal activities of 1b,2b and 3b compounds.

Bacteria (ORGANISM)	Zone of inhibition in mm				
	Chloramphenicol	CONTROL (DMSO)	1b	2b	3b
Escherichia coli	27	-	13	10	10
Pseudomonas aeruginosa	37	-	23	30	30
Staphylococcus aureus	31	-	19	25	20
Fungus (ORGANISM)	Ketoconazole				
Aspergillus niger	17	-	-	9	-
Candida albicans	15	-	-	7	6
Candida tropicalis	12	-	-	7	-

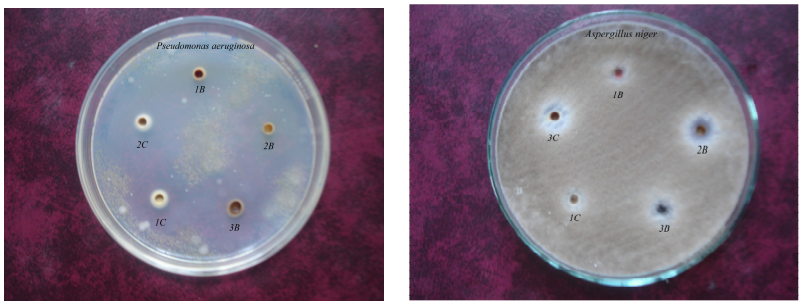


Fig.-1: Antibacterial and antifungal activities of 1b,2b and 3b compounds. (Selected Organism only shown)

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REFERENCES

1. M .R . Grimmett, Comprehensive Heterocyclic Chemistry, A. R. Katcizky, C .W. Rees, E .F. Scriven, Eds. Pergamon: Oxford, **3**, 77(1996).
2. J .V .Greenhill, L .Lue, Progress in Medicinal Chemistry, G.P. Ellis, D .K. Luscombe, Eds. Elsevier: New York**, 3**, 170(1993).
3. P. N .Preston, *Chem. Rev.,* **74**, 179(1974).
4. F. Touzeau, A .Arrault, G .Guillaumet, E .Scalbert, B. Pfeiffer, M .C. Rettori, P .Renard J .Y .Merour ,*J. Med.Chem.*, **46**, 1962(2003).
5. F. Roundu, G. L. Bihan, X .Wang, A .Lamouri, E .Touboul, G .Dive, T .Bellahsene, B .Pfeiffer, P. Renard, B. Guardiola- Lemaitre, D .Maneche , L .Penicaud, A .Ktorza , J. J .Godfroid, *J. Med. Chem.*, **40**, 3793(1997).
6. P .N .Preston, M.F .Stevens , G .Tennant ,Benzimidazoles and Congeneric Tricyclic Compounds, Part 2, John Wiley & Sons: New York (1980).
7. R. Cedillo-River , O .Munoz , *J. Med. Microbiol.,* **37**, 221(1992).
8. B .Chavez, R .Cedillo-Rivera , A. Martiner-Palomo ,*J. Protozool.,* **39**, 510(1992).

9. G. Navarrete-Vazquez, R .Cedillo, A .Hernandez-Campos, L .Yepez, F .Hernandez-Luis, J.Valdez , R. Morales Cortes, M .Hernandez , R .Castillo,*Bioorg. Med. Chem. Lett.*,**11**, 187(2001).
10. A. Strecker, *Ann. Chem. Pharm.,***75**, 27 (1950).
11. Y. Shafran, M. Bakulev, V. A. Mokrushin , *Russ. Chem. Rev.*, **58**, 148(1989).
12. (a) L. M. Weinstock, P. Davis, B .Handelsman, R .Tull, J. Org. Chem., **32**, 2823(1967);(b) W. L. Matier, Owens, D. A. Comer, W. T. Deitchman, D. Ferguson, H. C. Seidehamel,*J. Young, J. Med. Chem.*, **16**, 901 (1973).
13. (a) K. Mai, G. Patil, *Tetrahedron Lett.*, **125**, 4583 (1984);(b) S. Harusawa, Y. Hamada, T. Shiori, *Tetrahedron Lett.*, **20** , 4663 (1979); (c) M. S. Iyer, M. Gigstad, N. D. Namdev, M. Lipton, *J. Am. Chem. Soc.* , **118**, 4910(1996);(d) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.*, **120**, 5315 (1998);(e) M. Takamura, Y. Hamashima, H. Usuda, M. Kanai, M. Shibasaki, Angew. Chem., *Int. Ed. Engl.*, **39**, 1650 (2000)(f) S. Kobayashi, T. Busujima, S. Nagayama, *J. Chem. Soc., Chem. Commun.*, 981 (1998).
14. N. M. Leonard, L. C. Wieland, R. S. Mohan, *Tetrahedron* , **58**, 8373(2002).
15. W.Kromer, *Digestion*, **56,** 443(1995).
16. C. Perez , M. Pauli , P. Bazerque , *Acta Biology Medical Experiment*, **15**, 13(1990).

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