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Synthesis and Characterization of 2-(α-p -Substituted phenyl-α-benzimidazolo) methyl benzoxazole

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Abstract: 2-p-substituted phenyl-2-benzimidazolo acetonitriles (1a-5a) were prepared by the reaction of benzimidazole , p-substituted benzaldehydes and Sodium cyanide. A series of 2-(α-p -Substituted phenyl-α-benzimidazolo) methyl benzoxazoles (1b-5b) were synthesized by the reaction of 2-p-substituted phenyl-2-benzimidazolo acetonitrile(1a-5a) and o-aminophenol in presence of Conc. HCl. These compounds were characterized by IR , NMR and Mass spectroscopy.

Key words: Benzimidazole, o-aminophenol, acetonitrile, benzoxazole

Introduction

Heterocycles form by far the largest of classical divisions of organic chemistry and are of immense importance biologically and industrially. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic while countless additives and modifiers used in industrial applications ranging from cosmetics, reprography, information storage and plastics are heterocyclic in nature.

The importance of imidazoline and benz imidazloes, 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].

Almost all benzimidazole derivatives with their two ring systems bear different functional substituent 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[10]

A series of benzimidazole derivatives have proven anti-ulcer activity as potential inhibitors of H^+/K^+ -ATPase. Therapeutic significance of these clinically useful drugs in treatment of peptic ulcer and associated gastrointestinal diseases encouraged the development of some more potent and significant compounds [11]. These observations inspired us to synthesize the 2-(α-p -Substituted phenyl-α-benzimidazolo) methyl benzoxazoles.

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-d6) on a Varian EM-390 spectrometer using TMS as an internal standard (chemical shift in δppm). 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. The necessary chemicals were obtained from Merck and Fluka. All compounds showed satisfactory elemental analyses.

1.Synthesis of 2-p-substituted phenyl-2-benzimidazoloacetonitriles (1a-5a)

1.1.Synthesis of of 2-benzimidazolo-2-phenylacetonitrile (1a)

To a stirred solution of sodiumbisulphite (4.16 g ; 0.04 mol) in 10 mL of water benzaldehyde (4.24 g; 0.04 mol) was added and then benzimidazole (4.72 g; 0.04 mol) was added. The reaction mixture was stirred for 30 minutes and cooled in ice bath. A solution containing 1.96g (0.04 mol) of sodium cyanide was added dropwise into it . After 10 h the product was separated and filtered . The crude was recrystallized from chloroform-petroleum ether mixture. The pure sample melted at 183-184 ^{0}C.

1.2. Synthesis of 2-p-chlorophenyl-2-benz imidazoloacetonitrile(2a)

The 2-p-chlorophenyl-2-benzimidazolo acetonitrile (2a) was prepared by the reaction of p-chlorobenzaldehyde and benzimidazole in presence of NaH SO_4 as described above. The crude was recrystallized from chloroform-petroleum ether mixture .The pure sample melted at 158-159 ^{0}C.

1.3. Synthesis of 2-p-hydroxyphenyl-2-benzimidazoloacetonitrile(3a)

The 2-p-hydroxyphenyl-2-benzimidazoloacetonitrile(3a) was synthesized by the reaction of p-hydroxybenzaldehyde and benzimidazole. The crude was recrystallized from benzene-petroleum ether mixture . The pure compound melted at 192-193 ^{0}C.

1.4. Synthesis of 2-p –N, N'-Dimethylanilino -2-benzimidazoloacetonitrile(4a)

The 2-p –N, N'-dimethylanilino -2-benzimidazoloacetonitrile(4a) was synthesized by the reaction of p –N, N'-dimethylaminobenzaldehyde and benzimidazole. The crude was recrystallized from benzene-petroleum ether mixture . The pure compound melted at 137-138 ^{0}C.

1.5. Synthesis of 2--p-Anisyl-2-benzimidazolo acetonitrile (5a)

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.

2. Synthesis of 2-(α-p -Substituted phenyl-α-benzimidazolo) methyl benzoxazoles(1b-5b)

2.1. Synthesis of 2-(α-Benzimidazolo-α-phenyl) methyl benzoxazole (1b)

A mixture of 2-benzimidazolo-2-phenylacetonitrile (4.66g; 0.02mol) and o-aminophenol(2.18g; 0.02 mol)was taken in a 100mL round bottomed flask. Added 5mL of concentrated hydrochloric acid and was heated for 12 hours 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 hydrochloride was suspended in acetone and it was made alkaline by adding strong ammonia solution .The base was liberated by diluting it with water .The benzoxazole was filtered, washed with excess of water and dried. It was recrystallized from methanol . The pure sample melted at 195-197 ^{0}C.

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

3429 (m) 3366(m) 3181 (m) 3116(m) 2950 (w) 2924 (w) 2853 (m) 2050(m) 1920 (m) 1816 (m) 1799 (s)1750 (s) 1700 (m) 1665 (w) 1568 (s) 1477 (s) 1291 (m) 1266 (m) 1240 (m) 1169(m) 1100(s) 1066 (w) 1025 (w) 966 (m) 928 (w) 852 (m) 755(s) 683 (w) 613 (w) 569 (m) 447(w)

Proton Magnetic Resonance Spectral Data (CDCI3 / TMS), δ in ppm

4.6	s	1H	C-H methine
7.1-7.3	m	13H	Aromatic protons
8.1	s	1H	C –H benzimidazole

Mass Spectral Values ; m/z and %

325 (30) 324 (25) 297 (6) 284 (24) 248 (40) 235(42) 233 (28) 208 (20)
206 (100) 205 (65) 158 (48) 156 (32) 131 (15) 192 (32) 128 (10) 118 (10) 117
(50) 116 (20) 92 (45) 91 (35) 90 (55) 89 (20)63 (28)

Elemental Analysis	**C %**	**H%**
C_{21} H $_{15}$ N_3 Calculated :	77 .53	4.61
M.W . 325 found :	77.10	4.52

2.2. Synthesis of 2-(α-p Chlorophenyl -α – benz imidazolo) methyl benzoxazole(2b)

To a mixture of 2-p-chlorophenyl-2-benzimida zoloacetonitrile (5.34g;0.02mol) and o-amino phenol (2.18g; 0.02mol) , 5mL of concentrated hydrochloric acid was added. It was heated for 12 hours in an oil bath, maintained at 150-160^{0}C. The reaction mixture was kept overnight and the precipitated hydrochloride was filtered. It was washed using ethanol- ether mixture (1:5) and the hydrochloride was suspended in acetone. It was made alkaline by adding strong ammonia solution .The base was liberated by diluting with excess of water. The crude product was washed with water, dried .It was recrystallized from methanol. The pure sample melted at 180-182^{0}C.

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

3432(m) 3036 (m) 2924 (w) 2853 (w) 2750 (w) 2699 (w) 2432 (w) 2366 (m) 1715 (m) 1649 (m) 1588 (w) 1571 (s) 1520 (w) 1480 (s) 1400 (m) 1366(w) 1289 (s) 1215(m) 1177(m) 1140(m) 1100(m) 1090 (w) 1023 (w) 930(w) 855(s) 755(s) 666(m) 632(m) 574(s) 453(w)

Proton Magnetic Resonance Spectral Data (CDCI3 / TMS), δ in ppm

4.3 s 1H C-H methine

6.7-7.2 m 12H Aromatic protons

8.1 s 1H C –H benzimidazole

Mass Spectral Values ; m/z and %

360(25) 359(10) 319 (8) 285 (12) 270 (60) 268 (30) 257 (5) 248(35) 243(100) 241 (20) 236 (16) 230 (5) 229 (48) 228 (10) 213 (12) 203(25) 158 (55) 156(42) 130(38) 124(45) 119(60) 118 (18) 117 (8) 112(15) 92 (30) 91(45) 90 (65) 63 (28)

Elemental Analysis	**C %**	**H%**
$C_{21}H_{14}N_3CI$ Calculated :	70.09	3.89
M.W . 359 found :	70.00	3.75

2.3. Synthesis of 2-(α-p Hydroxyphenyl -α – benzimidazolo) methyl benzoxazole(3b)

A mixture of 2-p-hydroxyphenyl-2-benzimidazoloacetonitrile (4.98g;0.02mol) and o-aminophenol(2.18g; 0.02mole) was taken in a 100mL round bottomed flask and 5mL of concentrated hydrochloric acid was added. It was heated for 12 hours in an oil bath maintained at 150-180^{0}C. The reaction mixture was kept overnight and the precipitated hydrochloride was filtered. It was washed using ethanol- ether mixture (1:5) and the hydrochloride was suspended in acetone .It was made alkaline by adding strong ammonia solution . The base was liberated by diluting with excess of water. The crude product was filtered, washed with water, dried . It was recrystallized from benzene . The compound melted at163-165^{0}C.

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

3775(w) 3448 (w) 3083 (m) 2924 (m) 2854 (m) 2743 (s) 2666(w) 2583 (w) 1833(w) 1699 (s) 1632 (w) 1571 (s) 1472 (s) 1420 (s) 1410 (w) 1393 (m) 1301 (m) 1288 (m) 1250 (s) 1203 (w) 1168 (w) 1135 (w) 1049 (w) 1023 (w) 928 (w) 852 (m) 756 (m) 615 (w) 570 (m) 449 (w)

Proton Magnetic Resonance Spectral Data (CDCI3 / TMS), δ in ppm

4.6 s 1H C-H methine

6.7 -7.3 m 12H Aromatic protons

7.8 s 1H - OH phenolic

8.1 s 1H C –H benzimidazole

Mass Spectral Values ; m/z and %

343 (20) 342 (10) 341 (25) 324 (18) 323 (40) 297 (12) 286 (15) 256 (8) 248 (100) 236 (16) 224 (65) 222(20) 205 (28) 180 (10) 178 (24) 168 (25) 158(24) 156 (36) 150 (30) 149 (6) 132 (12) 131 (20) 127 (18) 120 (40) 119 (45) 118 (60) 117 (30) 105(15) 92 (35) 91 (10) 90(28) 63 (44)

Elemental Analysis	**C%**	**H%**
$C_{21}H_{15}N_3O_2$ Calculated :	73.9	4.39
M.W . 341 found :	72.5	4.23

2.4. Synthesis2-(α-p –N, N'-Dimethylanilino -α – benzimidazolo) methyl Benzoxazole (4b)

2-p-N,N'-Dimethylamino-2-benzimidazoloacetonitrile (5.52g;0.02mol) was mixed with o-aminophenol (2.18g; 0.02mol) and taken in a 100mL round bottomed flask. About 10mL of concentrated hydrochloric acid was added and it was heated for 12 hours in oil bath at 150-160^{0}C until the evolution of ammonia gas ceased . The reaction mixture was kept overnight. The precipitated hydrochloride was filtered,

washed with ethanol- ether mixture (1:5) and transferred to a beaker. The resulting hydrochloride was suspended in acetone and made alkaline with strong ammonia solution .The base was liberated by diluting with excess of water. The resulting solid was filtered, washed with water, dried .It was recrystallized from methanol. The pure sample melted at 141-142^{0}C.

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

3416 (m) 3382(w) 3066(m) 2925 (w) 2852 (w) 2500 (m) 1850 (w) 1750 (w) 1670 (m) 1620 (s) 1603 (w) 1589 (w) 1516 (m) 1466 (w) 1420(m) 1409 (s) 1356(m) 1232 (w) 1177 (m) 1123 (w) 1059 (w) 1019(w) 944 (m) 866 (w) 813 (w) 742 (s) 700 (w) 616 (w)566(w)

Proton Magnetic Resonance Spectral Data (CDCI3 / TMS), δ in ppm

2.9	s	6H	-N -(CH_3) $_2$
4.6	s	1H	C-H methine
6.7 -7.7	m	12H	Aromatic protons
8.1	s	1H	C –H benzimidazole

Mass Spectral Values ; m/z and %

368 (30) 367 (50) 324 (48) 278(45) 276 (25) 251 (20) 249(40)248 (30) 247 (12) 207 (15) 205 (20) 161(20) 159(25) 156 (40) 131 (35) 129 (15) 120 (30) 119 (60) 118 (100) 117 (15) 92(35) 91(22) 63 (40)

Elemental Analysis	**C %**	**H%**
C_{23} H $_{20}$ N_4 O Calculated	: 75.00	5.4
M.W . 368 found	: 74.9	5.2

2.5. Synthesis of 2-(α-p Anisyl-α – benzimidazolo) methyl benzoxazole (5b)

A mixture of 2-p -Anisyl-2 –benzimidazolo acetonitrile (5.26g;0.02mol)and o-aminophenol(2.18g; 0.02mol)was taken in a 100mL round bottomed flask. Added about 5mL of concentrated hydrochloric acid it was heated for 10 hours in an oil bath maintained at 150-160^{0}C until the evolution of ammonia gas ceased. The reaction mixture was kept overnight .The precipitated hydrochloride was filtered, washed with ethanol ether mixture (1:5) and transferred to a beaker. The resulting hydrochloride was suspended in acetone and made alkaline with strong ammonia solution .The base was liberated by diluting with excess of water . The resulting solid was filtered, and washed with water and dried. It was recrystallised from chloroform. The pure sample melted at 125-126^{0}C.

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

3416 (m) 3376 (m) 3066(w) 2949 (w) 2925 (m)2853 (m) 2799 (w) 2449 (w) 1783 (m) 1742 (s) 1620 (s) 1580 (s) 1480(s) 1397 (w) 1295 (m) 1252 (s) 1172(m) 1132 (w) 1026 (m) 926 (w) 850 (w) 831(w) 753 (m) 704 (w) 634(w) 567 (m) 450(m)

Proton Magnetic Resonance Spectral Data (CDCI3 / TMS), δ in ppm

3.9	s	3H	-OCH_3
4.6	s	1H	C-H methine
6.7 -7.7	m	12H	Aromatic protons
8.0	s	1H	C –H benzimidazole

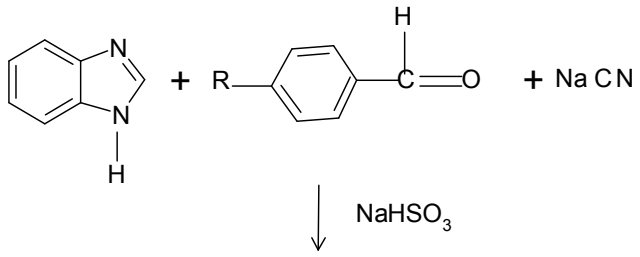
Mass Spectral Values ; m/z and %

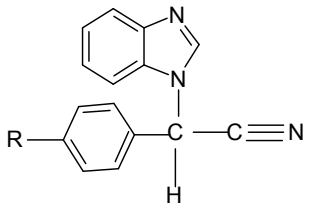
355 (40) 354 (18) 324 (28) 285 (12) 265 (35) 263 (42) 248 (36)238 (55) 236(45) 158 (40) 156 (20) 146(25) 144(16) 129 (38) 119 (20) 118 (28) 117 (30) 107(18) 92 (50) 91 (100) 90(28) 63 (35)

Elemental Analysis	**C%**	**H%**
C_{22} H $_{17}$ N_3 O Calculated	: 74.36	4.78
M.W . 355 found	: 73.52	4.52

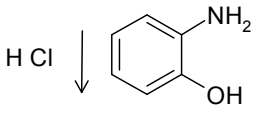
Table 1: Spectral data of the compounds (1a-5a)

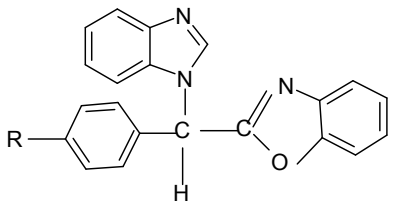
Sample No	IR (KBr) cm $^{-1}$ (Nitriles)	^{1} H-NMR ($CDCl_3$) δ ppm
1a	2230	4.6(S,1H, -CH methine),7.0-7.4 (m,9H,Ar-H), 8.2(s,1H,C-H, Benzimidazole)
2a	2240	4.6(s,1H, -CH methine),7.0-7.4 (m,8H,Ar –H), 8.2(s,1H,C-H, Benzimidazole)
3a	2220	4.6(S,1H, -CH methine),6..6-7.4 (m,8H,Ar-H),7.8, (S, 1H,OH Phenolic),8.1(s,1H,C-H, Benzimidazole)
4a	2240	3.0 (s,6H-N -(CH_3) $_2$) 4.6(s,1H, -CH methine), 6.6-7.3(m,8H,Ar-H),8.2(s,1H,C-H, Benzimidazole)
5a	2232	3.9(s,3H, - CH_3 anisyl) 4.6(s,1H, -CH methine), 7.0-7.4 (m,8H,Ar-H),8.2(s,1H,C-H, Benzimidazole)





(1a-5a)





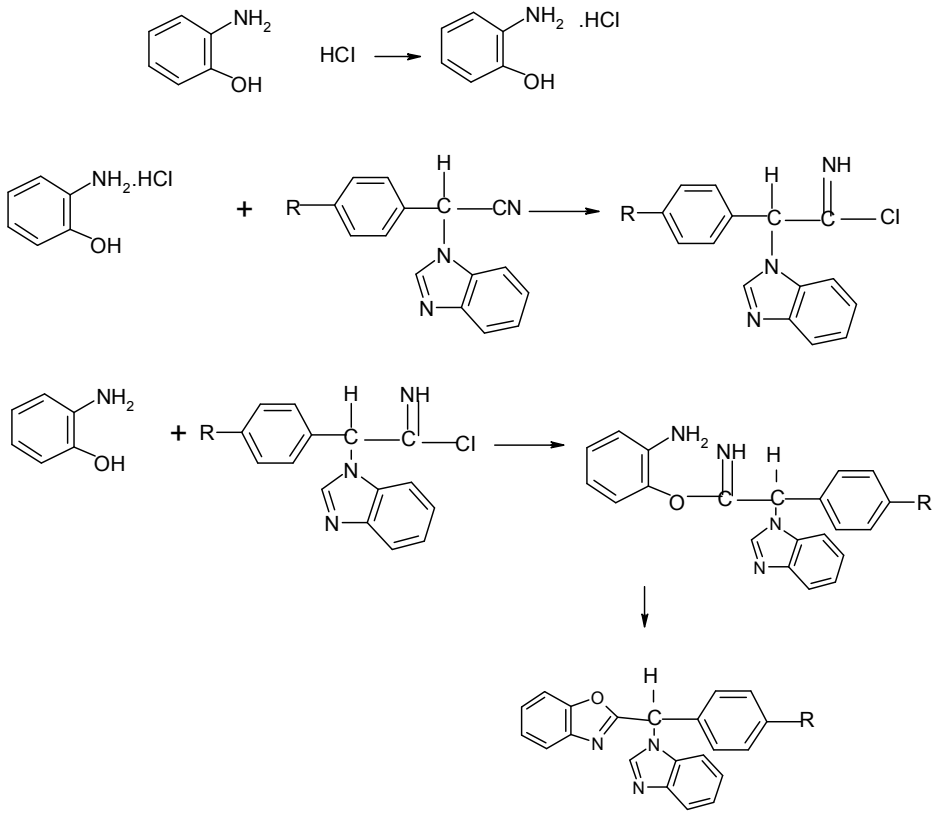
(1b-5b)

R = H , CI , OCH_3 ,OH, -N –$(CH_3)_2$

Scheme-1: **Synthesis of 2-(α-p -Substituted phenyl-α-benzimidazolo) methyl benzoxazoles**

Results and Discussion

The formation of 2-p-substituted phenyl-2-benz imidazolo acetonitriles (1a-5a) was confirmed by spectral values of IR and NMR and are presented in **Table 1**. In the present study, 2-(α-p -Substituted phenyl-α-benzimidazolo) methyl benzoxazoles were synthesized by condensation of 2 -benzimidazolo -2-phenylacetonitrile(1a) and other nitriles(2a-5a) and o-aminophenol in the presence of hydrochloric acid . The synthetic route of these compounds were represented as **Scheme-I.** Nitriles make ring closure in the presence of acids[12] and it follows the mechanism:



R = H , CI , OCH_3 ,OH, -N $(CH_3)_2$

References

1. Grimmett M R, In *Comprehensive Heterocyclic Chemistry,* Katcizky A R, Rees C W, Scriven E F V, Eds, Pergamon: Oxford,1996, **3 ,** 77-220 .
2. Greenhill J V, Lue L, *In Progress in Medicinal Chemistry,* Ellis G P, Luscombe D K, Eds, Elsevier: New York, 1993,**3**, 170-180.
3. Preston P N, *Chem. Rev.*1974*,* **74,** 179-314 .
4. Touzeau F, Arrault A, Guillaumet G, Scalbert E, Pfeiffer B, Rettori M C, Renard P and Merour J Y *J. Med.Chem..*2003, **46,** 1962-1979 .
5. Roundu F, Bihan G L, Wang X, Lamouri A, Touboul E, Dive G, Bellahsene T, Pfeiffer B, Renard P, Guardiola- Lemaitre B, Maneche D,Penicaud L, Ktorza A and Godfroid J J, *J. Med. Chem.*1997, **40,** 3793-3803.
6. Preston P N, Stevens M F G and Tennant G *Benzimidazoles and Congeneric Tricyclic Compounds*, Part 2, John Wiley & Sons: New York , 1980.
7. Cedillo-River R and Munoz O *J. Med. Microbiol,*1992, **37**, 221-224 .
8. Chavez B, Cedillo-Rivera R and Martiner-Palomo A *J. Protozool,*1992, **39**, 510-515.
9. Navarrete-Vazquez G, Cedillo R, Hernandez-Campos A, Yepez L, Hernandez-Luis F, Valdez J, Morales R Cortes R Hernandez M and Castillo R *Bioorg. Med. Chem. Lett.* 2001,**11,** 187- 190 .
10. W.Kromer, *Digestion*,1995, **56,** 443-454 .
11. Avinash Pati , Swastika Ganguly and Sanjay Surana , Rasayan J. Chem . 2008,1(.3), 447-460 .
12. Holljes E L, and Wagner E C, J. Org. Chem.,1944, **9**,31 .

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