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Synthesis & Biological Evaluation of Some Novel Mannich Bases of Benzimidazole Derivatives

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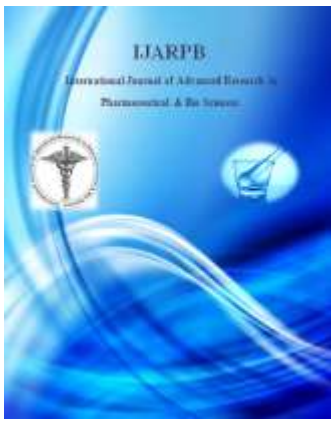

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ABSTRACT

Benzimidazoles are weakly basic, being some what less basic than the imidazoles. Benzimidazoles are also sufficient acidic to be generally soluble in aqueous alkali and form N-metallic compounds. The acidic properties of benzimidazoles, like those of imidazoles seem to be due to stabilization of the ion by resonance. Those compounds possessing unsubstituted –NH grouping show molecular association through N-H-N bonds. The dipole moment of benzimidazole has been determined to be 3.93D (in dioxane) and 4.08D. The benzimidazole ring possesses a high degree of stability. Benzimidazole, for example, is not affected by the concentrated sulfuric acid when heated under pressure to 270^{o}C, or by vigorous treatment with hot hydrochloric acid or with alkalis.

KEY WORDS-Carbamazepine,Oxcarbazepie,Benzimide,Valporic acid.

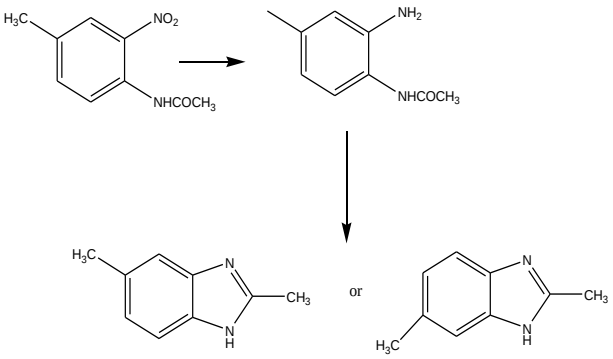
INTRODUCTION

The benzimidazoles contain a phenyl ring fused to an imidazole ring as indicated in the structure. This important group of substances has found practical applications in a number of fields. Benzimidazole, which is a heterocyclic nucleus, plays an important role in various medicines.[2]In early 1950s the vital role of purines in biological systems was established and it was discovered that 5, 6-dimethyl-1-(α-D-ribofuranosyl) benzimidazole is an integral part of the structure of Vit. B_{12}[3]. The discovery that 5, 6-dimthylbenzimidazole moiety is part of chemical structure of vitamin B_{12} has prompted a massive research upon benzimidazoles with particular emphasis on the synthesis of new compounds for pharmacological screening.

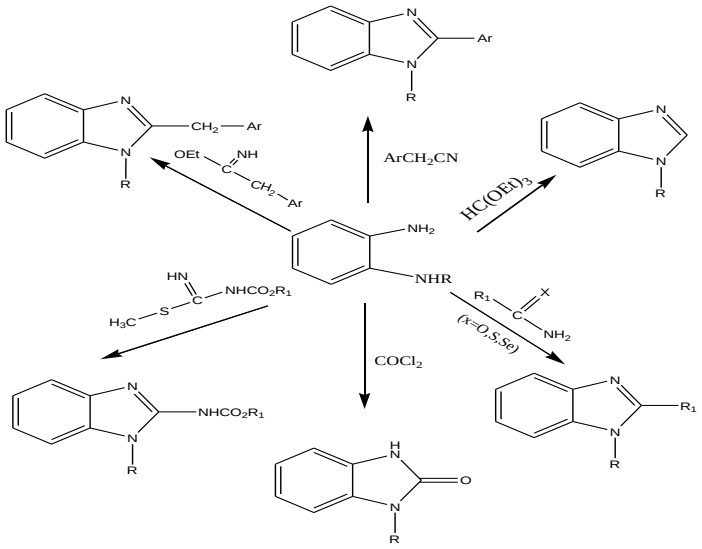
These findings stimulated great interest in the chemistry of imidazoles and related compounds, and considerable commercial success has accrued from these studies: a new antibacterial agent [azomycin], a trichomonacide [metronidazole] and a variety of benzimidazole derivatives are used as anthelmintic agents [e.g. thiabendazole] and fungicides [e.g. benomyl] are well established marketed products.A number of therapeutic agents such as H_1 antihistaminic agent clemizole, a potent opioid analgesic etonitazene, non-nucleoside antiviral compound enviroxime, for promotion of excretion of uric acid irtemazole, non sedating antihistaminic agent astemizole, anti ulcer drugs omeprazole and pentoprazole, antihelmintic thiabendazole, antinematodal nocodazole etc. are based on benzimidazole heterocyclic nucleus. Benzimidazole undergoes a number of reactions such as electrophilic and nucleophilic addition, thermal oxidation and electrocyclic reactions.The discovery that 5, 6-dimthylbenzimidazole moiety is part of chemical structure of vitamin B_{12} has prompted a massive research upon benzimidazoles with particular emphasis on the synthesis of new compounds for pharmacological screening[2-3].

HISTORY

Historically, the first benzimidazole was prepared in 1872 by Hoebrecker, who obtained 2, 5 or (2, 6)-dimethyl benzimidazole by the reduction of 2-nitro-4-methylacetanilde. Since compounds of this type were formed by the loss of water, they were called “anhydrobases”.

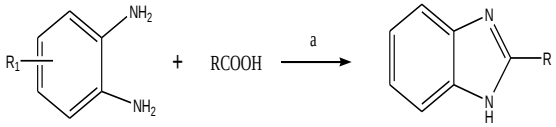


The benzimidazole is also called as 1,3-benzodiazole, azindole, benzoglyoxaline, 3-azaindole, 1H-benzimidazole, o-benzimidazole, BZI, 1, 3-diazaindene, NSC 7591 with melting point of 170-172^{o}C and occurs as white crystals. It is highly stable, combustible but incompatible with strong oxidizing agents. It is harmful if swallowed, inhaled or absorbed through the skin. It is used as muscle relaxant.

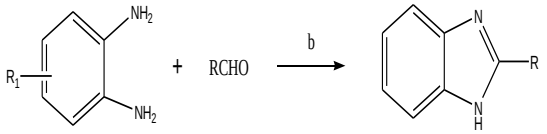


Methods of preparation of benzimidazole derivatives

For the synthesis of benzimidazoles, o-phenylenediamine is reacted with chloroacetic acid and leads to the formation of chloromethylamide which further cyclizes to form 2-chloromethylimidazole. Pyrrolidine displaces the halogen and affords alkylation product. The alkylated product so formed on treatment with sodium hydride removes fused proton with imidazole nitrogen which on further treatment with 4-dichloro-toluene gives H_1 antihistaminic agent clemizole. Aromatic nucleophilic displacement of highly activated chlorine in 2, 4-dinitrochlorobenzene by means of N,N-diethyl- ethylenediamine gives corresponding aniline. Treatment with ammonium sulfide leads to selective reduction of nitro group adjacent to newly introduced amino group to form diamine. Then, the formed diamine is condensed with iminoether from 4-ethoxyphenylacetonitrile leads to benzimidazole ring formation[4]. In general, benzimidazoles are prepared by the condensation of o-phenylenediamine with carboxylic acids under harsh dehydrating conditions[5-7].



The catalyst may be used are Conc. HCl, polyphosphoric acid or alumina-methane sulfonic acid.[8] Benzimidazoles are also prepared by the condensation of o-phenylenediamine with various aldehydes.



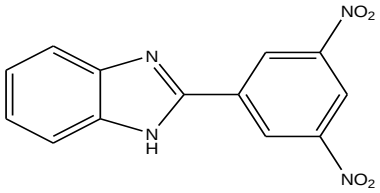
The catalyst may be used are sodium metabisulfite[9], polyethyleneglycol (PEG),[10] amonium acetate.[11]Various 1 and 2-substituted benzimidazoles can also be prepared by following scheme[12].

General Methodology Experimental Compound:

Synthesis of 2-(3,5-Dinitrophenyl)-1*H*-benzo[*d*]imidazole (compound A)

O-Phenylenediamine (7.56gm, 0.07mole) and 3, 5-Dinitrobenzoic acid (14.84gm, 0.07 mole) in 140 ml glacial Acetic acid were refluxed on water bath for 85 min. The reaction mixture was allowed to cool and precipitate so obtained was

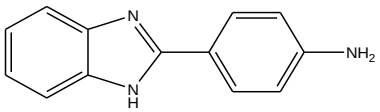
filtered off and washed with cold water. The crude product was recrystallized with 10% glacial acetic acid. The completion of reaction was monitored by running TLC. Solvent system: Ethyl acetate: Methanol: Chloroform (4:3:3).



2-(3,5-Dinitrophenyl)-1*H*-benzo[*d*]imidazole

Synthesis of 4-(1*H*-Benzo[*d*]imidazol-2-yl)benzenamine (compound B)

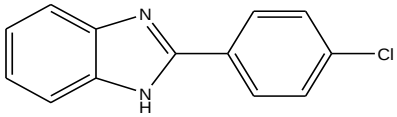
O-Phenylenediamine (7.56gm, 0.07mole) and 4-Aminobenzoic acid (9.59gm, 0.07mole) in 140 ml glacial Acetic acid were refluxed on water bath for 100min. The reaction mixture was allowed to cool and precipitate so obtained was filtered off and washed with cold water. The crude product was recrystallized with 10% glacial acetic acid. The completion of reaction was monitored by running TLC. Solvent system: Ethyl acetate: Methanol: Chloroform (4:3:3)

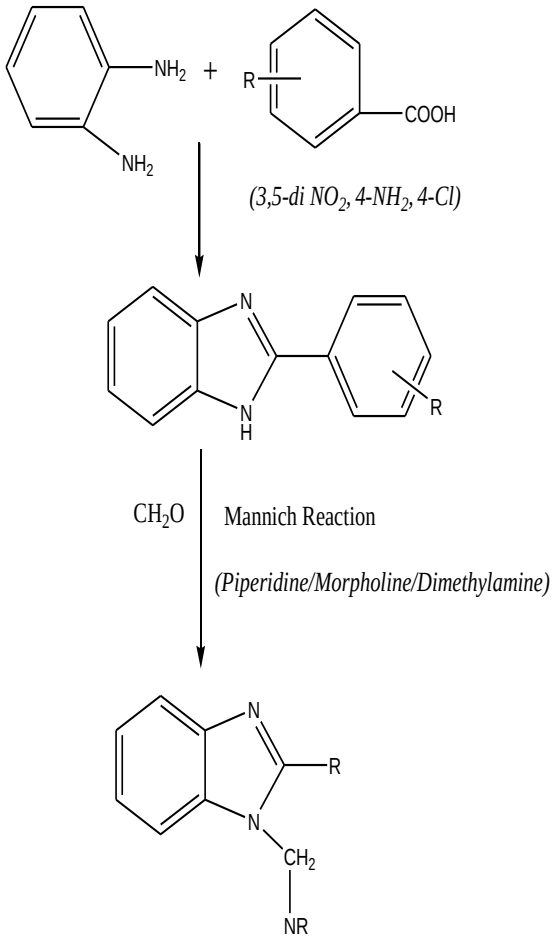


4-(1*H*-Benzo[*d*]imidazol-2yl)benzenamine (compound B)

Synthesis of 2-(4-Chlorophenyl)-1*H*-benzo[*d*]imidazole (compound C)

O-Phenylenediamine (7.56gm, 0.07mole) and 4-Chlorobenzoic acid (10.92gm, 0.07mole) in 140 ml glacial Acetic acid were refluxed on water bath for 90min. The reaction mixture was allowed to cool and precipitate so obtained was filtered off and washed with cold water. The crude product was recrystallized with 10% glacial acetic acid. The completion of reaction was monitored by running TLC. Solvent system: Ethyl acetate: Methanol: Chloroform (4:3:3)





General Methodology Scheme-1

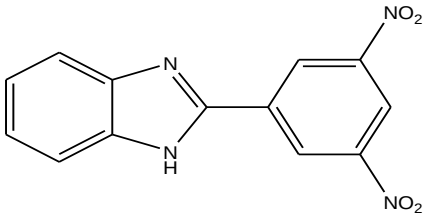
TABLE 1: THE PHYSICO CHEMICAL DATA OF SYNTHESIZED COMPOUND

Comp.	M. F.	Yield (gm)	Mol. Wt.	R_f	Color (Appearance)	m.p. (^{0}C)
A	$C_{13}H_8N_4O_4$	4.2	284	0.74	Orange	230
B	$C_{13}H_{11}N_3$	4	209	0.72	Cream	171
C	$C_{13}H_9N_2Cl$	4.12	228	0.78	Yellowish White	193

TABLE 2: IR DATA OF THE TITLE COMPOUND

Comp.	Wave Number in cm^{-1}
A	3284.88(Sec.NH), 2951.19(Ar-CH), 1595.18, 1606.76 (Ar-NO_2), 1383.01(tert.N)
B	3319.60 (sec.NH), 2951.19(Ar-CH), 1595.18, 1577.82 (Ar-NO_2), 1369.50(tert.N), 1230.63(C-O-C)
C	3184.58(sec.NH), 2955.04(Ar-CH), 1591.33, 1616.40 (Ar-NO_2), 1369.50(tert.N)

TABLE 3: ^{1}HNMR (ppm) DATA OF THE TITLE COMPOUND

Comp.	Compound	^{1}HNMR (ppm)
A		7.66 – 7.20 (m, 7H, Ar-H) 4.69 – 4.68 (m, 2H, CH_2) 2.88 – 2.32 (m, 10H)

Biological Activity of Hydrazone Compounds:

Anti-Convulsant Activity: Different types of epilepsies, i.e. grand mal, petit mal or psychomotor type, can be studied in laboratory animals. The maximal electro-shock (MES)-induced convulsions in animals represent grand mal type of epilepsy. Similarly, chemo-convulsions due to PTZ which produce clonic–type of convulsions resemble petit mal type of convulsions in man. There are the two procedures used to study convulsions, and to test anticonvulsant drugs in laboratory animals. In MES-convulsion electroshock is applied through the corneal electrodes. Through optic stimulation cortical excitation was produced. The MES-convulsions are divided into five phases such as (a) tonic flexion, (b) tonic extensor, (c) clonic convulsions, (d) stupor and (e) recovery or death.

TABLE 5: ANTICONVULSANT ACTIVITY

COMPOUND	MEAN±SEM	% PROTECTION
Control (DMSO)	8.840± 0.159	0.0
Phenytoin sodium	1.760± 0.05099	80.00
A1	6.840± 0.1364	22.62
A2	5.460± 0.1077	38.23
A3	2.980± 0.1428	66.28

RESULT AND DISCUSSION

The synthesis of the title compounds were affected as outlined in the scheme, the substituted benzimidazole was prepared by refluxing o-phenylenediamine with substituted benzoic acid in acetic acid. Then the mannich base of substituted benzimidazole were synthesized by various 2° amine to yield compound A, B,and C and were characterized by M.P. and T.L.C., I.R.,^{1}HNMR., and mass spectra. All the synthesized title compounds were subjected for *in-vivo* anticonvulsant activity. The results showed that mannich bases of Dimethylamine have shown to posses significant reduction in the seizures. The *in-vivo* anticonvulsant activity was determined as extensor phase duration by Maximal shock method rats using phenytoin sodium as reference standard and the results showed that compound A, B, C were active against seizures induced by electric shock.

REFERENCE:

1. Abraham DJ, Burger's Medicinal Chemistry and drug discovery, John Wiley. 2003, 6, 180.
2. Preston PN, Synthesis, reaction and spectroscopic properties of benzimidazoles Chem. Rev. 1974, 74(3), 279.
3. Humaira A, Synthesis and characterization of potentially bioactive nucleosides bearing different heterocyclic moieties, Ph.D Thesis Department of Chemistry, Quaid-i-Azam University, Islambad, 2006.
4. Singh J, Goyal A, and Pathak DP, Benzimidazole: heterocyclic nucleus. *Indian J. Pharm. Educ. Res.* 2006, 40(3), 147-152.
5. Mills K, and Joule J, A. Heterocyclic Chemistry, Black well Publishing, 2000, 4, 454-517.
6. Thomas LG, Heterocyclic Chemistry, Pearson Education, 2007, 83, 311-317,341.
7. Bansan RK, Heterocyclic chemistry, synthesis, reaction & mechanism, Willey Estern Limited, 1990, 320.
8. Oztekin A, Kaessler A, Apcin Y, Yilmaz A, and Joachim J, Comparative studies on conventional and microwave synthesis of some benzimidazole, benzothiazole and indole derivatives and testing on inhibition of hyaluronidase. *Molecules.* 2008, 13, 736-748.
9. Kumar J R, Jawahar LJ, and Pathak DP, Synthesis of benzimidazole derivatives: as anti-hypertensive agents, *E.Journal of Chemistry*, 2006, 3,278-285.
10. Mukhopadhyay C, and Tapaswi PK, PEG-mediated catalyst-free expeditious synthesis of 2-substituted benzimidazoles and bis-benzimidazoles under solvent-less conditions, *Tetr. Lett.* 2008, 49, 6237–6240.
11. Sharghi H, Asemani O, and Khalifeh R, New One-Pot Procedure for the Synthesis of 2-Substituted Benzimidazoles, *Synthetic Communications*, 2008, 38, 1128–1136, 2008.
12. Grimmett MR, Imidazole and Benzimidazole synthesis, Department of Chemistry, Acedemic Press Publication, 1997, 1, 227.