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Review Article

BENZIMIDAZOLE : AN OWERVIEW

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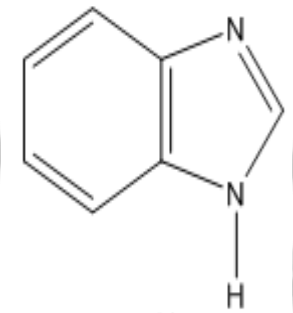
Abstract

Benzimidazole nucleus is one of the most important heterocycles exhibiting remarkable pharmacological activities. Numerous method for the synthesis of benzimidazole and also their diverse reactions offer enormous scope in the field of medicinal chemistry. The utility of benzimidazole as synthon for various biologically active compounds has given impetus to these studies. The present review provides a broad view of the synthesis, properties and biological activity possessed by compounds having benzimidazole nucleus.

Keywords: - : Benzimidazole, Heterocyclic, Properties and Biological activity .

INTRODUCTION

Benzimidazole (I) is a heterocyclic aromatic compound. It consists of a benzene ring fused with an imidazole ring at its 4, 5- positions. The various positions on the benzimidazole ring are numbered in the manner indicated , with the imino function as number one.



(I)

Structure of Benzimidazole

Benzimidazoles possessing free imino hydrogen are tautomeric systems. The two possible tautomeric forms of benzimidazole and of those of its derivatives possessing a plane of symmetry are identical, and a definite assignment of structure is possible.

Mankind has been in constant search for antibacterial agents to combat the various infections that has taken millions of lives over the years.

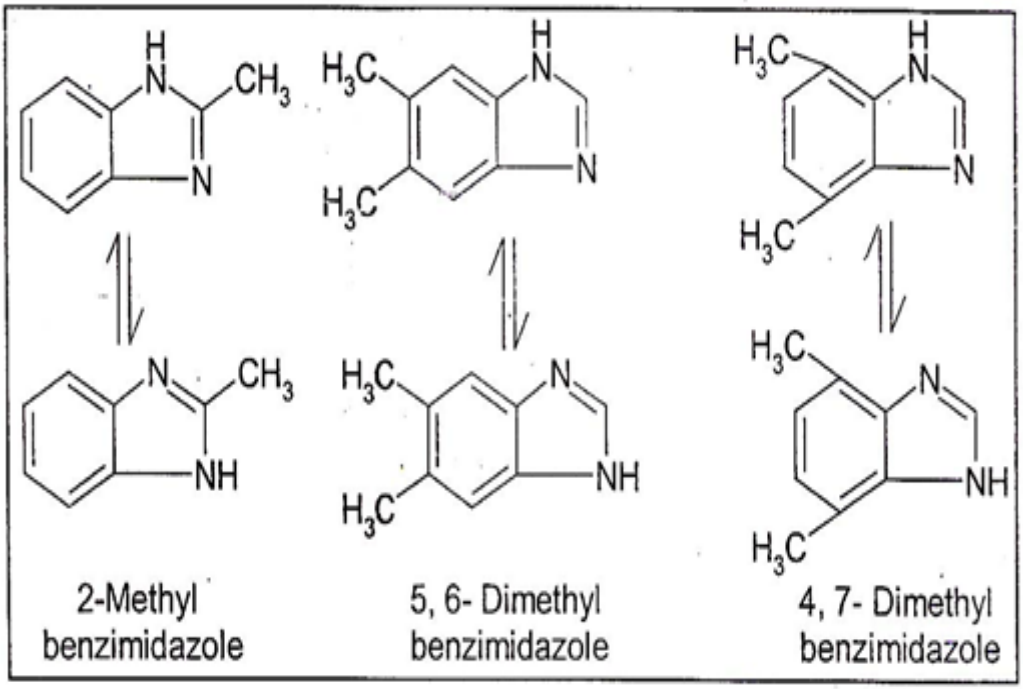
Selective toxicity, the property of certain chemicals to destroy one form of life without harming another. is the cornerstone of modern antimicrobial chemotherapy. The concept is largely credited to Paul Ehrlich, who discovered the selective -staining properties of certain antibacterial dyes and the anti parasitic activity of organic arsenicals. Although the compounds discovered by Ehrlich has largely been replaced by safer and more effective agent, his ideas paved the way for the advent of the sulfonamides and penicillin and elucidation of the mechanism for their selective toxicity. The modern era of the chemotherapy of infection started with the clinical use of sulfanilamides in 1936. The golden age of anti¬microbial therapy began with the production of penicillin on 12th Feb. 1941. In rapid succession, deliberate searches of the metabolic products of the wide variety of soil microbes led to discovery of streptomycin (1943), chloramphenicol (1947), chlortetracycline(l948), neomycin(1949), erythromycin (1952), and more, and this ushered in the age of the miracle drugs.

In 20th century there was significant achievement in discovery and commercial development of various antibacterial agents that provide effective treatment for many infections and diseases that has previously caused extensive mortality, morbidity and fear.[2]Benzimidazole derivatives are of wide interest because of their diverse biological activity and clinical applications. This heterocyclic ring system is present in numerous anti-parasitic. Fungicidal. Anthelminitc and

anti-inflammatory drugs[3,4,5,6]. Substituted 2-trifluorobenzimidazoles are potent decouplers of oxidative phosphorylation in mitochondria. These compounds also inhibit photosynthesis and therefore exhibit appreciable herbicidal activity[7] .their antibacterial and antifungal activity was also observed[8,9] .Most recently. Antiprotozoal activity of 2- trifluoromethylbenzimidazoles in particular that of their chlorosubstituted derivatives was reported[10]. Which is consistent with earlier observations of antigiardial activity of various benzimidazole derivatives[11,12].

Mono- and polysubstituted benzimidazoles not possessing a plane of symmetry may as though they were composed of two compounds, thus rendering impossible a definite assignment of structure. for example: 4 methyl benzimidazole is tautomeric with 7-methyl benzimidazole and consequently, must be designed as 4 – (or –7) methyl benzimidazole.

Substitution of the imino hydrogen eliminates the possibility for tautomerism, and a definite assignment of structure becomes possible. The number starts at the substituted nitrogen.

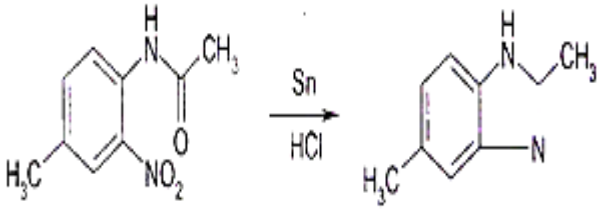


Tautomeric forms of Benzimidazoles

A) Routes For Benzimidazole Nucleus Formation

From Acylated O-Nitroarylamines:

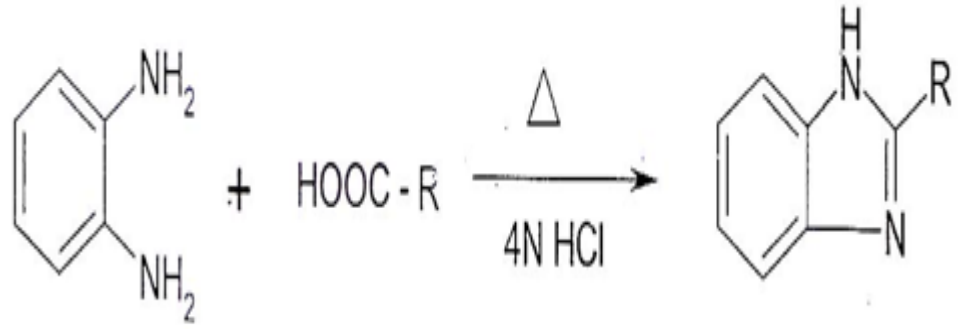
Hobrecket in 1872 reduced 2 – nitro 4- methyl acetanilide with tin and hydrochloric acid and obtained 2, 5- (or 2, 6-) dimethyl benzimidazole[1].



From o-phenylenediamines and Carboxylic acids, Acid ahhydrides , Esters or Amides:

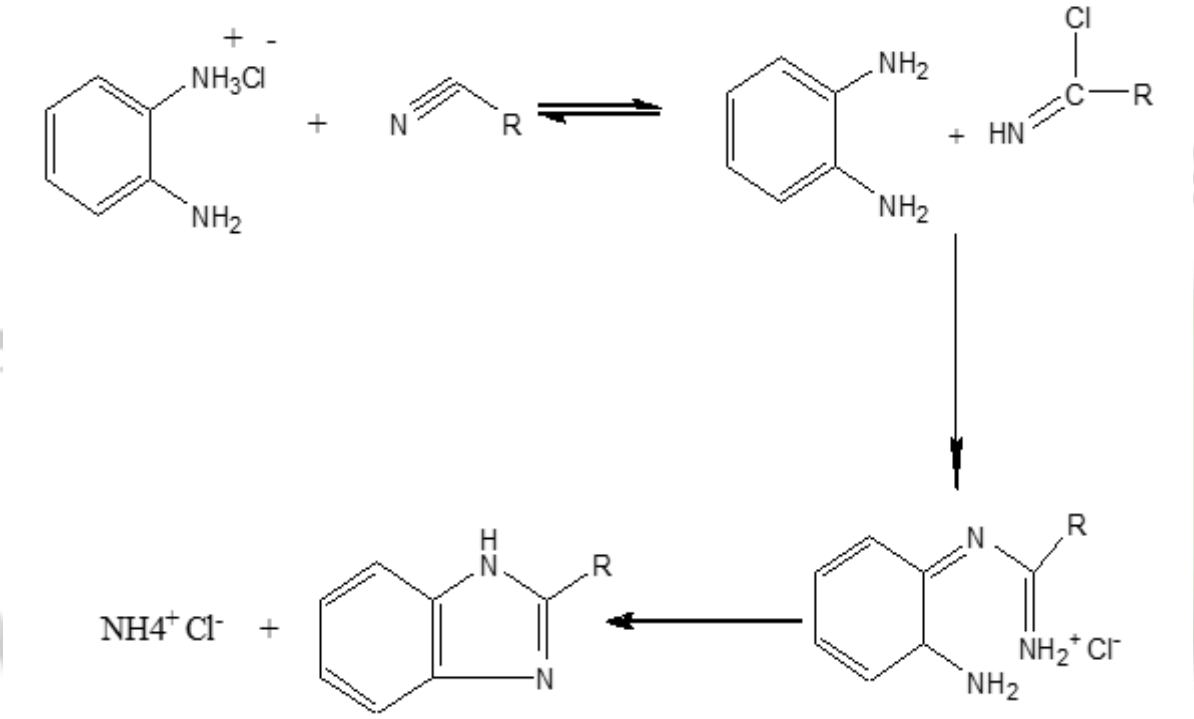
Ladenburg refluxed a glacial acid solution of 3, 4-diaminotoluene and obtained 2, 5- (or2,6-) dimethyl which is of great practical importance[13].

Philips developed an excellent method for the preparation of benzimidazoles which involves refluxing an equimolar mixture of an o- phenylenediamine and a carboxylic acid or an acid anhydride in dilute. Hydrochloric acid (4N HCI is usually employed). This is frequently referred to as Phillip's benzimidazole synthesis[14].



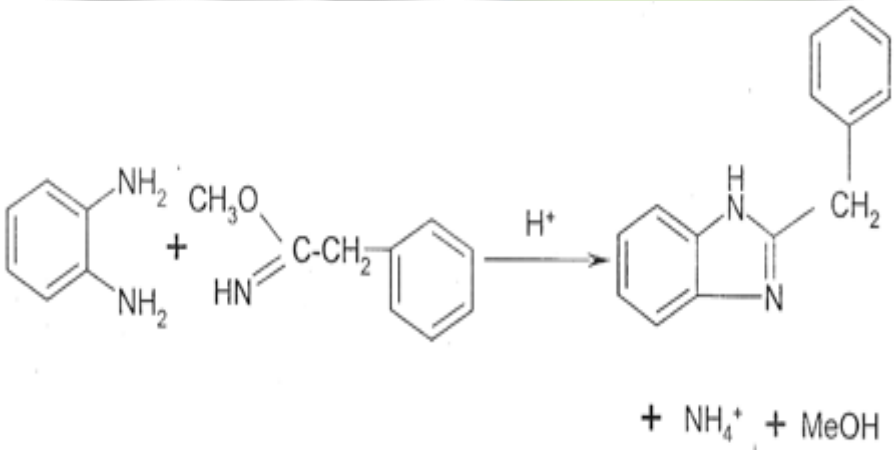
Form o-phenylenediamines and nitrites:

Wagner prepared 2- substituted benzimidazole by heating the monohydrochloride of o- phenylenediamine with an aliphatic or an aromatic nitrile at 2000 C.



From o-Phenylenediamines and Imin ethers or Imino ethers or Imino thioethers:

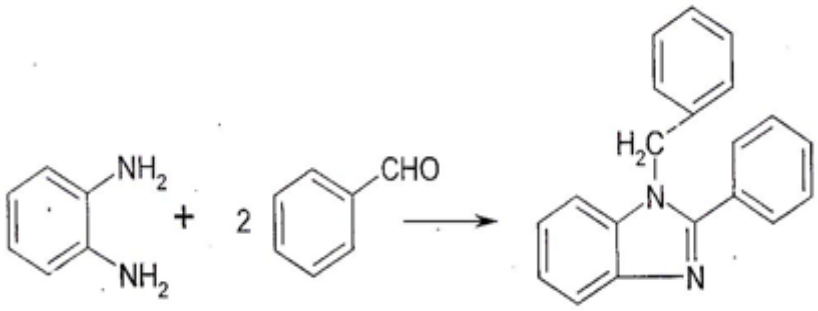
The interaction of o-phyenylenediamine and an iminoether or an imino thioether provides another convenient route to a benzimidazole.



The formation of phyenyl benzimidazole from o-phenylenediamine and phenacetamino methyl etheryl serves an illustration The reaction is acid catayzed[15].

From o-Phenylenediamines and Aldehydes or Ketones:

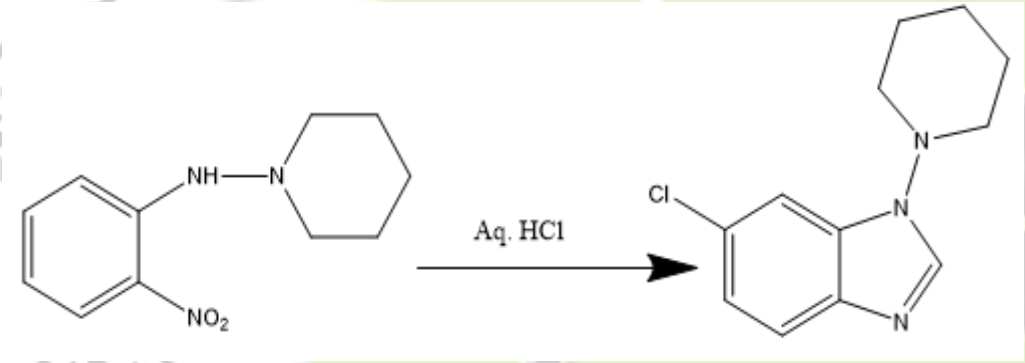
Aldehydes react with o- phenylenediamine or substituted 0- phenylendiamine with the formation of benzimidazoles (aldehydes)



The reaction discovered Ladenburg and is referred to as the "aldehydine" synthesis. For example, the aldehydine resulting from the interaction or o- phenylenediamine and benzaldehyde is 1- benzyl-2- phenyl benzimidazole[16].

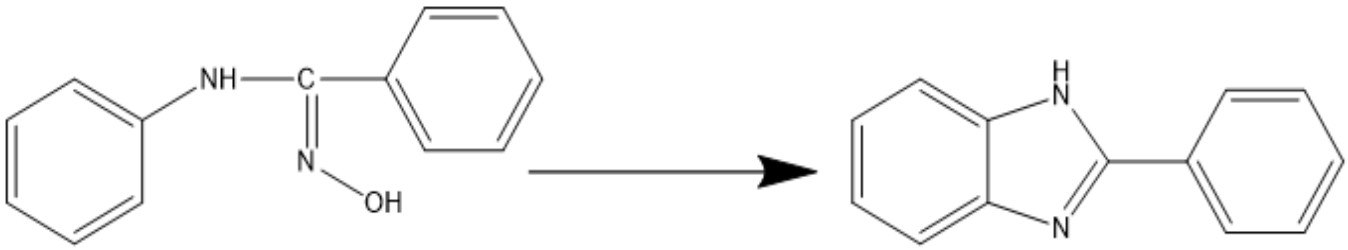
From O-nitro aryl amines and O-Dinitroarenes

The synthesis of benzimidazole from O-nitro aryl amines and O-dinitroarenes is an acid catalyzed cyclization reaction. In this N-(O-nitroanilino)- substituted amines are cyclized to N-aminobenimidazoles under reflux in aqueous hydrochloric acid.



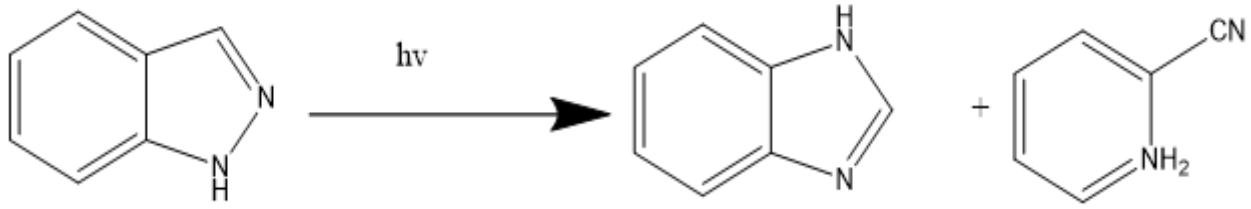
From Amidines and Related Compounds

The formation of benzimidazoles from N-aryl amidines is obtained by reacting it with benzenesulfonyl chloride in triethylamine under anhydrous condition.



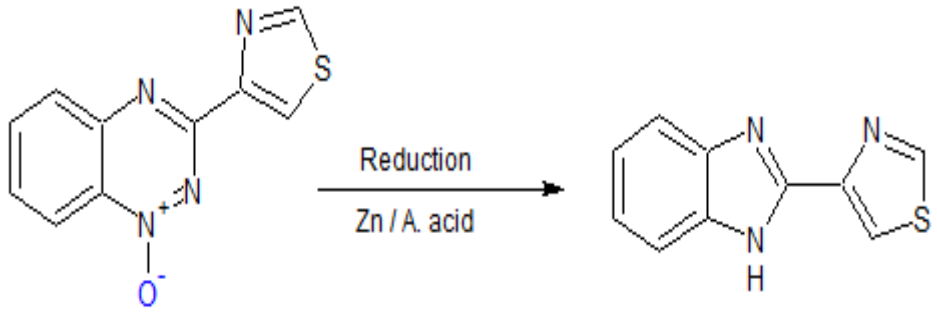
From Five-Membered Ring Heterocycles

Benzimidazole is formed in good yield by photolysis of indazoles.



From Six-Membered Ring Heterocycles

Benzimidazole and its 1-methyl derivative are obtained in 100 and 50% yields, respectively. By allowing O-phenylene diamine or N-methyl-O-phenylene diamine to react with S-triazine at temperature just over the melting point of diamine.



1.3. PROPERTIES[17]

1.3.1Physical Properties

Benzimidazoles are high melting and high boiling point solids. The parent compound melts at 1700C. They are soluble in polar and sparingly soluble in nonpolar solvents. Substitution of the imino hydrogen markedly lowers the boiling and melting points.

1.3.2.Chemical Properties

Benzimidazole (pKa 5.5) is a base considerably weaker than imidazole (pKa 7.0).This is a reflection of the conjugation between the imidazole and benzene rings. Conjugation increases the number of contributing states in the resonance sense, thus enhancing the chemical stability of the molecule due to their chemical stability (aromatic character), benzimidazoles are resistant to the most drastic treatments with acids and bases, and are not readily attacked by oxidizing agents. The chemical reactivity of benzimidazole is governed by the functional behaviour of the nitrogens (salt formation, acylation and alkylation) and its ability to undergo electrophillic substitution in the benzene ring.

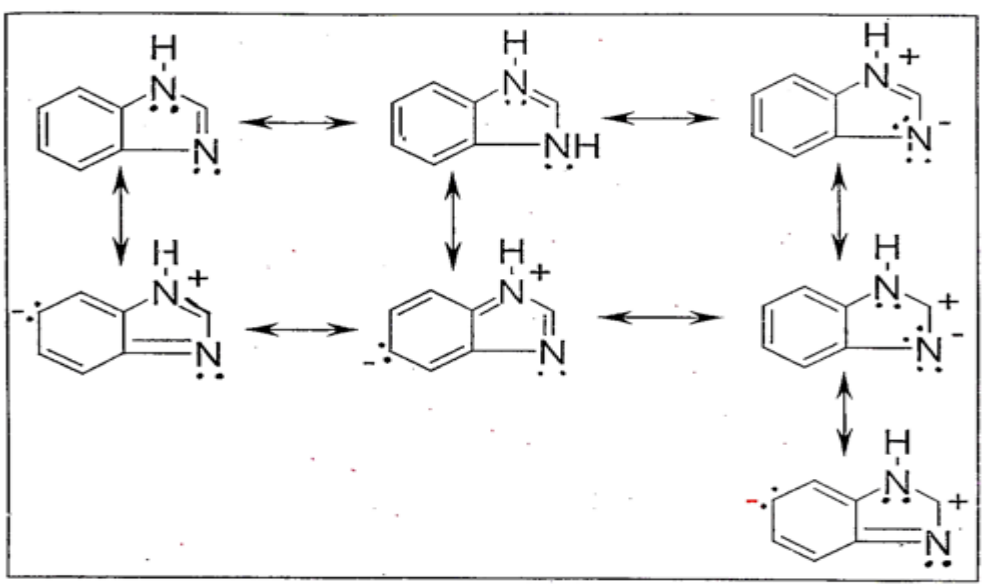
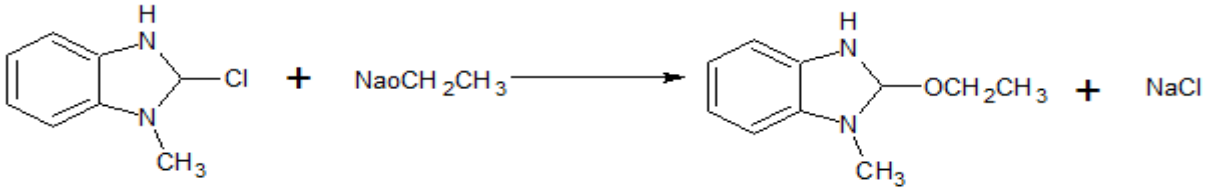


Figure : Various Resonance Forms of Benzimidazole

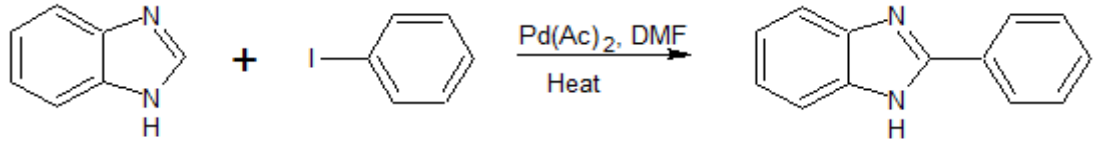
Nucleophilic substitution in the imidazole ring:

The chichibabin reaction is used for the synthesis of a number of 2-aminobenzimidazole derivatives. For unsubstituted 2-halobenzimidazole a competition exist between proton abstraction by the nucleophile at the 1 position with concomitant retardation of 2-substitution. Accordingly chloride ion is not displaced from 2-Chlorobenzimidazole by powerful nucleophiles. Whereas, 2-Chloro-1-mehtyl benzimidazole reacts readily with sodium methoxide or ethoxide.

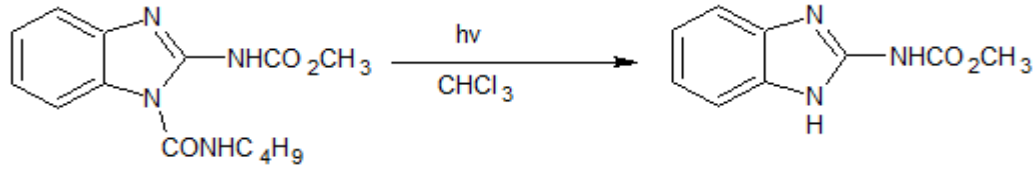


Reaction involving Aryens and Free radicals

Benzimidazole reacts as a nucleophile with benzyne to give 2-phenyl benzimidazole.

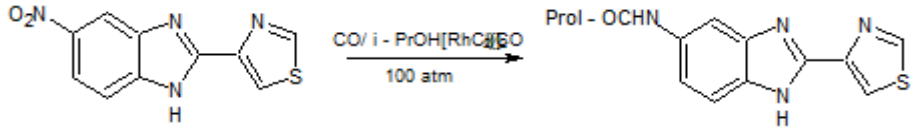


Benzimidazole reacts with free radicals by thermal or photochemical methods.



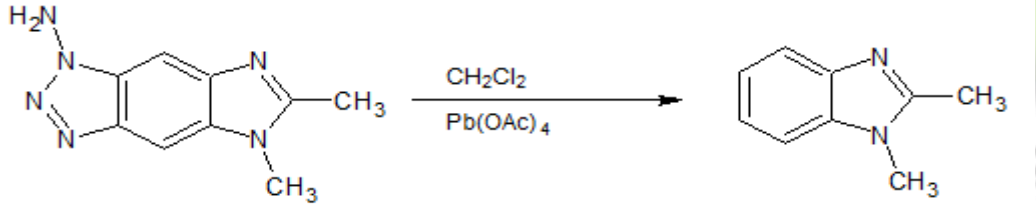
Reduction

The standard method for reduction of benzimidazole involves hydrogenation in the presence of a platinum catalyst in acetic acid, palladium used.



Oxidation

Oxidation is carried out in hydrogen peroxide, lead oxide, lead tetra acetate and chromic acid.



1.4. Physiological Action Of Benzimidazoles

Benzimidazole inhibits the growth of certain yeasts and bacteria.[18] This action is reversed by the addition of adenine of adenine or guanine. It was noted, however, that adenine does not "benzimidazole anesthesia" in mice so that the latter effect is apparently not purine utilization. The antagonistic or inhibiting action of benzimidazole, which is reversed by adenine or guanine, is not surprising in view of the structural similarities of the two systems. Substitution of an amino group in the benzene nucleus of benzimidazole does not appear to affect the inhibiting action to any extent. Both the 4-amino- and 5-amino -benzomidazoles have been prepared by vander Want.[19] Substitution on the 2-carbon atom is reported to decrease the activity. Presumably replacement of the hydrogen on the 1-(3)-nitrogen atom would destroy the activity, since the – NH – group of the imidazole group is apparently involved in attachments to enzyme systems. Benzimidazole has also been reported to inhibit virus production in tissue cultures.[20] Alkyl-substituted benzimidazoles have been shown to inhibit the multiplication of influenza B virus, Lee strain.[21] Benzimidazole is reported as being a more active ant thyroid agent in rats than phenylthiourea.[22] The 2-alkylaminomethyl and 2-dialkylaminomethyl benzimida-zoles possess local anesthetic activity.

The relative activities of these compounds appear to be dependent on the nature and size of the alkyl group present. The is some indication that these compounds possess some analgesic activity also.[23]

1.5. BIOLOGICAL ACTIVITIES

Benzimidazole nucleus is an important heterocycle present in a large variety of biologically active compounds, many among which are clinically used. Banzimidazole derivatives possess broad spectrum of biological activities like anticancer, anti-inflammatory, antimicrobial and antiviral., anthelmintic, analgesic, antihistamine, psychopharmacological[24].

CONCLUSION:

The analytical and other informational data, available in literature so far, have rendered benzimidazole significantly important class of heterocyclic compounds and their applications in ever challenging chemotherapy of various ailments/ infections etc. since last two decades immensely hiked interests of medicinal chemist and biochemist.

This particular review article, in reference, would extend great deal of help to researchers in reckoning and determining the best and most productive, economical, suggestive and conclusive access to various benzimdazole of clinical importance superseding other compounds of their class.

REFERENCE:

1.A Pandey & Aparna Shukla; Indian J.Chem. dec.1999, 38B, 1381-1383.

2.A. H. Leeman, M. L. Hammond, M. Maletic, G. M. Bantorelli., S. F. Waddell., J. Finn, M. Marytko, S. Ram and d. Keith. PCT INT. Wo 2000. 0066. 119 (chem.. Abstr. 2000. 133. 350507)

3.A. Ladenburg, ibid., 10, (1887) 1123.

4.A. Orjales. V. Rubio and M. Bordell. Eur. Pat .EP 1998. 8

8. 4545 (Chem. Abstr. 1998.128. 140702).

5.A. puratchikody, V. sivajothi, A, jaswanth, k. Ruckmani and M. Nallu; Indian J. Het. Chem.. Jan-March 2002, 11, 241-242.

6.Arnold R Martin , " Anti infective agents: in Wilson and Gisvolds textbook of Organic Medicinal & Pharmaceutical Chemistry, 9th editiom. 1991; 129 – 186: J.N. Delgado.,

7.W.A. Remers (Eds.)7.B. Alici, Y. Gok, R. Durmaz and S. guanl , J . Chemother. 1999. 11. 83.

8.Baiola Andrzejewska, lilian yepez-mulia, Roberto Cedillo- Rivera & Zygmunt kazimierczuk; Eur. J. Med. Chem. . 2002, 37, 973-978.

9.Bywater ,McGinty, and jenesel, J. Pharmacol. , 84, 342 (1945): 85, 14 (1945).

10.Cory r. Theberge, A. Mccaulcy, Joseph J. Ramano 2004, 47, 2089-2096

11.D. kumar , M. R. Jacob, M.B. Reynolds and S. M. Kerwin. Bioorg. Med. Chem. 2002. 10 3997.

12.D.E. Burton , A.J. Lambie, J.C. Ludgate, G.T. Newbold, A.Percival, D.T. Saggers, Nature (London) 208 (1965) 1166-1170.

13.E. Cetinkaya. B. Alici, Y. Gok, R. Durmaz and S. guanl , J . Chemother. 1999. 11. 83.

14.L. Xiao, K.Saeed, R.P.Herd, Vet. Parasitol. 61 (1996) 165-170.

15.F. E. King and R. M. Acheson, J. Chern. Soc., (1949) 1396.

16.F. Hobrecker, Ber. 5., (1872) 920.

17.G. Navarette – Vazquez, R.Cedillo –Rivera, A.Hernandez – Campos, L.Yetez – Mulia, F. Hernandez – Luis, J. Valdez , R. Morales, R. Cortes, M. Hernandez, R.Castillo, Bioorg. Med. Chem. Lett. 11 (2001) 187 – 190

18.H. Hall, N. J. Peaty, J. R. Henry, J. Easmon, G. Heinisch and G. purstinger. Arch. Pharm. (Weinheim). 1999. 332. 115.

19.H. L. Wheeler, Arnerican Chern. J., 17, (1895) 397.

20.I. Oren, . O. Temiz. I.Yalcin. E. Sener and N. altanlar, Eur. J. Pharm. Sci. 1999. 7,153..

21.Jan Koci, Milan pour & jiri Stachel Eur. J. Med. Chem. 2002, 37, 409-418.

22. John Mann, Anne Baron, Yaw Opoku-Boahen, Eric Johansson, Gary

23.L Hunter and J. A. Marriott, J. Chern. Soc., (1941) 777.

24.L. Garuthi, M. Roberti, T. Rossi, C. Cermelli, M. Portolani, M. Malagoli and M.Castelli, Anticancer Drug Design, 13 (1998) 397.

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