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NOVEL SYNTHESIS OF PHENYL ISOXAZOL-3-YL-5-METHOXY-1H-BENZOIMIDAZOLE AND ITS SUBSTITUTED DERIVATIVES

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Abstract :
Methyl 5-(4-substituted phenyl)isoxazole-3-carboxylate (1a-c) on reduction with $LiAlH_4$ gives 5-(4-substituted phenyl)isoxazole-3-carbaldehyde (2a-d). Which on refluxed with 4-methoxy benzene-1,2-diamine (3) in presence of DCE as a catalyst for 3-4 hours to obtain number of substituted derivatives of phenyl isoxazol-3-yl-5-methoxy-1H-benzoimidazole(4a-d) in very good yields.

Key Words :
DCE, 4-methoxy benzene-1,2-diamine, 5-(4-substituted phenyl)isoxazole-3-carbaldehyde.

Introduction :

Benzimidazole is as aromatic heterocyclic organic compound. The synthesis of benzimidazole based poly heterocycles draw the attention of pharmacists from last few decades as it functions as an important pharmacophore in medicinal chemistry and pharmacology. Basically, benzimidazole is a bicyclic compound consisting of the fusion of benzene with imidazole which ultimately gives a privileged structure. This magical moiety possesses many pharmacological properties. Till now the most prominent benzimidazole moiety is N-ribosyl dimethyl benzimidazole present in nature and it serves as the axial ligand for cobalt in vitamin B_{12}[1].

Benzimidazole possess many biological activities such as antimicrobial, anti-fungal, anti-histaminic, anti-inflammatory, antiviral, anti-oxidant, anti-cancer, anti-ulcerative etc., that's why benzimidazole derivatives are considered as an important moiety for the development of molecules of pharmaceutical interest.[2,3] There is biological relevance of many heterocyclic building blocks is due to the structural similarity to purine nucleobase and as benzimidazole derivative also which selectively inhibits the endothelial cell growth and then suppresses the process of angiogenesis in vitro as well as in vivo.[3]

Benzimidazole derivatives are of wide interest because of their diverse biological activity and clinical applications, they are remarkably effective compounds both with respect to their inhibitory activity and their favorable selectivity ratio.[4] Looking at the importance of benzimidazole and oxadiazole nucleus, it was thought that it would be worthwhile to design

and synthesize some new benzimidazole derivatives bearing oxadiazole moiety and screen them for potential biological activities. We have previously reported the synthesis of some new biologically active benzimidazoles. Resistance to number of anti-microbial agents (βlactam antibiotics, macrolides, quinolones, and vancomycin) among a variety of clinically significant species of bacteria is becoming increasingly important global problem.

In particular, increasing drug resistance among Gram-positive a bacterium such as staphylococci, enterococci, and streptococci is a significant health matter. Benzimidazole ring displays an important heterocyclic pharmacophore in drug discovery. These compounds carrying different substituent's in the benzimidazole structure are associated with a wide range of biological activities including anti-cancer, anti-viral, anti-bacterial, antifungal, anti-helminthic, anti-inflammatory, antihistaminic, proton pump inhibitor, anti-oxidant, Anti-hypertensive and anti-coagulant properties.[5] In 1960, Fort et al. reported the discovery of benzimidazole derivatives as proton pump inhibitors. Further, synthesis and evaluation of different substituted benzimidazole derivatives resulted in the discovery of omeprazole, lansoprazole, rabeprazole, and pantoprazole.[6]

Based on their broad biological functions,[7] they are used in clinical medicine[8] as anti-ulcer, anti-tumor and anti-viral agent[9]. They have Potential use for treatment of diseases such as ischemia-repression, injury[10] hypertension[11] and obesity[12]. Benzimidazole derivatives have been demonstrated to inhibit Picornaviruses[13], Polioviruses[14], Enteroviruses[15] etc. Broad antiviral applications of benzimidazole derivatives prompted us to synthesize various N-substituted and 2-substituted benzimidazole and evaluate their antiviral activities against Tobacco mosaic Virus and Sun hemp rosette virus. Several synthetic methodologies are available for the synthesis of benzimidazole. Generally, condensation of o-phenylene diamine with carboxylic acid carboxylic acid and their nitrile, imides and orthoesters[16].

Synthesis of 2-substuted benzimidazole from an appropriate o-phenylenediamine and ortho-ester such as orthoformate, orthoacetate and ortho-valerate using $ZrOCl_2.8H_2O$ at room temperature and under microwave irradiation[17]. Simple and efficient method for the convenient synthesis of 2-arylbenzimidazole on reaction with o-phenylenediamine and various aromatic aldehydes using cobalt (II) chloride hexahydrate as a catalyst[18].

An alternative synthetic approach using [Fe (III)/Fe(II)] redox mediate[19] oxidation of Schiff base intermediates derivative from o-phenylenediamines and various aromatic heterocyclic aldehyde gave the desire products. Synthesized differently substituted benzimidazole in very good yield in Solvent free conditions from o-phenylenediamine and aldehydes in presence of BF3OEt2 as a catalyst the method is applicable to aromatic, unsaturated and aliphatic aldehydes and to substituted o-phenylenediamines without significant difference[20]. Several of these reported procedures for the preparation of 2-substitited benzimidazole derivatives were neither versatile nor compatible with differently substituted starting materials. They are associated with many practical difficulties for example, use of high temperature for the polyphosphoric acid mediated condensation reaction led to the formation of by-products and benzimidazoles in low yield.

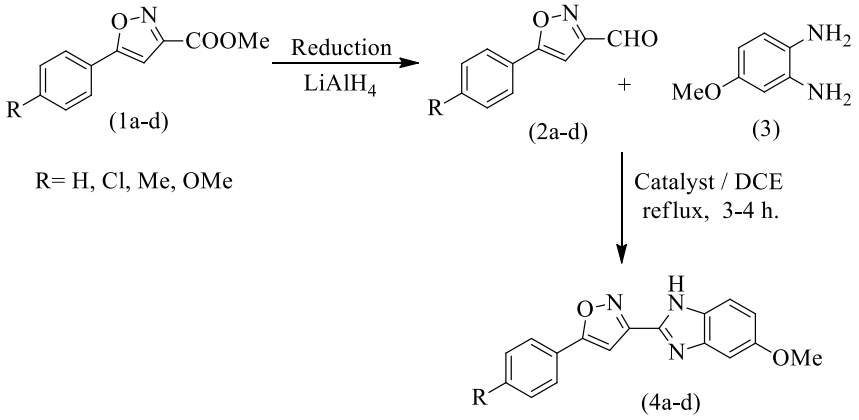
Experimental Section :

Melting points were determined in open capillary tube with anhydrous substance and were uncorrected. IR spectra of the newly synthesized compound were recorded with potassium bromide pellets technique, ^1H NMR spectra were recorded with the help of AVANCE 300 MHz Spectrometer in DMSO using TMS as internal standard. Mass spectra of the compound were recorded on a FT VG-7070H. Mass Spectrometer using EI technique at 70 eV is used. All the reactions of the newly synthesized were monitored by Thin layer chromatography.

Material and Methods :

Synthesis of substituted derivatives of phenyl isoxazol-3-yl-5-methoxy-1H-benzoimidazole (4a-d) :

Methyl 5-(4-substituted phenyl)isoxazole-3-carboxylate (1a-c) on reduction with $LiAlH_4$ gives 5-(4-substituted phenyl)isoxazole-3-carbaldehyde (2a-d). Which on refluxed with 4-methoxy benzene-1,2-diamine (3) in presence of DCE as a catalyst for 3-4 hours to obtain number of substituted derivatives of phenyl isoxazol-3-yl-5-methoxy-1H-benzoimidazole (4a-d) in very good yields (Scheme-1). This synthesis is novel in the sense that it preserves the simplicity, time consuming and improves the yields.



(Scheme-1)

Results and Discussion :

In order to synthesize substituted Benzimidazole derivatives (4a-d), a relatively more versatile yet simplified procedure was perceived. Our argument has been that an instantaneous condensation of o-phenalene diamine and 5-(4-substituted phenyl)isoxazole-3-carbaldehyde (2a-d) on refluxed with in presence of DCE as a catalyst for 3-4 hours to obtain number of substituted derivatives of phenyl isoxazol-3-yl-5-methoxy-1H-benzoimidazole (4a-d).

Conclusion:

In conclusion we have developed a simple methodology for the preparation of substituted Benzimidazole derivatives. The advantage of this method are extremely mild reaction conditions, short reaction time, high yield, simple experimental technique and compliance with green chemistry protocols.

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