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Synthesis, Characterization and Antibacterial Activity of Imidazole Derivatives

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ABSTRACT

Among the bioactive heterocyclic frameworks, nitrogen containing multisubstituted imidazoles are versatile building blocks of many naturally occurring products. In the present work, we have designed a procedure for synthesizing a biologically active imidazoles using Biodegradable Chitosan Catalyst. The synthesized compounds were characterized by IR, NMR, mass spectral. All the compounds were tested for antibacterial and antifungal activities. The antimicrobial activities of the compounds were assessed by Disc diffusion method.

Keywords : Antibacterial, Antifungal Activity, Imidazole, Chitosan

I. INTRODUCTION

Multicomponent reactions (MCRs), as an important organic synthesis approach, are one-pot processes, which involve reaction of three or more accessible components to form a single product that incorporates essentially most or all the atoms of the starting materials.[1] MCRs strategies grant remarkable advantages over conventional bimolecular reactions owing to their convergence, atom-economy, operational simplicity, structural diversity and short synthetic pathway.[2]MCRs have recently gained a new dimension in the field of designing methods to produce elaborate libraries of biologically active compounds and new molecular frameworks for potential drugs with diverse pharmacological activities.[3]Imidazole, a fundamental class of heterocycles, is a unique template of multifaceted applications. This nitrogen containing molecule is not only a natural motif (element of DNA base, histidine, alkaloids, biotin, vitamin B12, etc.) but also documented as plant growth regulators and pesticides in agriculture[4-5].The development of novel methods for the regiocontrolled synthesis of substituted imidazoles is of strategic importance. This is due to the preponderance of applications to which this important heterocycle is being deployed, such as the

traditional applications in pharmaceuticals and agrochemicals. [6-7]

Due to the peculiar structural characteristic of imidazole scaffold with a worthy electron-rich feature, it is advantageous for imidazole groups to combine with various receptors and enzymes in biological systems, through diverse weak interactions, thereby showing a variety of biological activities. At present, a legion of imidazole-containing compounds with high a medical potential as a clinical drug have been widely used to treat diverse types of illnesses, such as anti-inflammatory, antibacterial, anti-parasitic, antifungal, antiviral, antihistaminic, anticancer and enzyme inhibition. [8]In a related protocol, the reaction of N-iminylsulphilimine with amides was recently reported to afford 4-amino substituted imidazoles in good to excellent yields [9].In related work, Geng et. al. found that ketones and 2-aminobenzylalcohols could be reacted together in the presence of iodine, ferric chloride and toluenesulphonylmethyl isocyanide to afford 1,4-disubstitued imidazoles [10]

Marzouk et al. recently reported the preparation of $ZnFe_2O_4$ nanoparticles as well as their use as catalysts for the synthesis of substituted imidazoles [11]Similar approaches were recently reported by Thwin et al. who used a copper catalyst to facilitate formation of the imidazoles [12].A similar disconnection was undertaken by Varzi and Maleki in which a ZnS-$ZnFe_2O_4$ nanocatalyst was used to synthesize 2,4,5-trisubsttituted-NH-imidazoles. [13].Multisubstituted imidazoles are useful substrates in creation of molecules of biological or pharmaceutical interest. Different imidazoles have been synthesized via multicomponent reactions involving the condensation of aldehydes, 1,2-diketone, generally with ammonia as the nitrogen source. The activity of variety of heterogeneous catalysts was remarkably explored in achieving high selectivity and conversion rates. [14]Maleki et al. described highly efficient, green, and rapid protocol for the synthesis of 2,4,5-trisubstituted imidazoles through a three-component, one-pot condensation reaction of benzil, aromatic aldehydes, and ammonium acetate by using graphene oxide (GO)-chitosan bio-nanocomposite as a heterogeneous nano-catalyst.[15]

A novel heterogeneous biopolymer solid supported acidic catalyst, chitosan-SO_3H was reported by Khan et al. The high thermal stability of acid catalyst worked well in reaction between benzil, various aromatic aldehydes, ammonium acetate, and anilines with short reaction time with excellent yields in both microwave irradiation and conventional heating for the transformation to multisubstituted imidazoles[16] Safari et al. have reported the nano crystalline $MgAl_2O_4$ as a mild Lewis acidic heterogeneous mixed oxide catalyst for the three and four component condensation reactions to synthesize substituted imidazole derivatives. [17]Agarwal et al. have described highly versatile 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazole derivatives by using a zinc-proline hybrid material (ZnPHM) as an inexpensive Lewis acidic catalyst. The reported catalyst displayed efficient activity, good recyclability, cost-effectiveness, plus nontoxic and nonvolatile character[18].Among all the natural polymers, chitosan (CS) is one of the most promising biopolymers on the market. This is a well-known polysaccharide mainly produced from chitin, present in the cuticles of arthropods, the endoskeletons of cephalopods, and the cell walls of fungi. Composed of both 2-acetamido-2-deoxy-β-D-glucan and 2-amino-2-deoxy-β-D-glucan units, this linear copolymer has revealed very interesting physicochemical and biological properties for biomedical applications. [19]Chitosan molecule is a copolymer composed of Nacetyl-d-glucosamine and d-glucosamine units available in different grades depending upon the degree of acetylated moieties[20]

Saravanan and other synthesized 1-(4-(N,N-dimethylamino)phenyl)-2-phenyl-4-(4-(dimethylamino)benzylidene)imidazole-5-(4H)one were screened against the bacterial stains: Staphylococcus aureus and Bacillus pumilus found to have a significant higher antibacterial activity [21] the present work was aimed to synthesize imidazole derivatives expected to have antimicrobial activity.

II. METHODS AND MATERIAL

All the chemical of analytical grade. Benzil, 3-Chloro-4-methylbenzaldehyde, Ammonium Acetate(Sigma-Aldrich) were purchased from Sigma-Aldrich and used without further purification. IR Spectra recorded on Perkin Elmer Spectrometer in range 4000-400 cm-1 KBr pellets. Room Temperature magnetic moments by Guoy's method in B.M.Electronic Spectra using DMSO on Varian Carry 5000 Spectrometer. Molar Conductance measurements in dry DMSO having 1×10-3 concentration on Systronics conductivity bridge at room temperature. Elemental analysis (C, H, N) were carried out by using perkin Elmer 2400 elemental analyzer

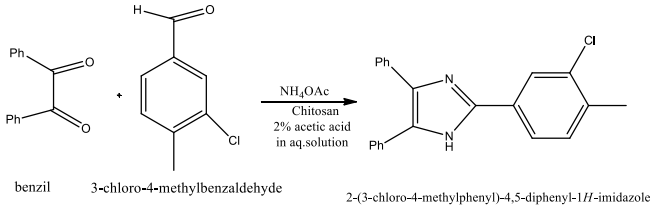
Antimicrobial Activity

2-(3-chloro-4-methylphenyl)-4,5-diphenyl-1H-imidazole was evaluated in vitro their antibacterial activity against two Gram-Positive bacteria,viz, *B. Subtilis*; *S. aureus,* Two fungal strains *A. niger* and *F. oxysporum* by Kirby-Bauer disc diffusion method[22].The experimental value compare with standard drug value Miconazole for the Antifungal activity and Ciprofloxacin for the antibacterial activity.

Synthesis of 2-(3-chloro-4-methylphenyl)-4,5-diphenyl-1H-imidazole

3-Chloro-4-methylbenzaldehyde (0.30g, 2 mmol), benzil (0.42 g, 2 mmol) and ammonium acetate (0.32 g, 4.2 mmol) were added in a round-bottom flask with 0.09g of chitosan in 2% aq.acetic acid solution[23]. The reaction mixture was stirred a room temperature for 5 min.Then reaction mixture was heated at 65-70°C for 4-5 hr. The reaction was allowed to cool to room temperature. The resulting precipitate was collected by filtration and washed with cold ethanol to afford the product. The crude product was purified by recrystallization from ethanol (Scheme.1).

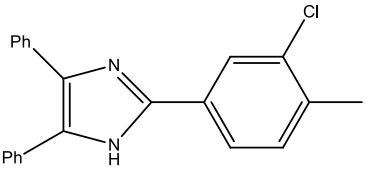
Scheme 1.Synthesis of Substitute imidazole



III.RESULTS AND DISCUSSION

2-(3-chloro-4-methylphenyl)-4,5-diphenyl-1H-imidazole is prepared (Table.1).Imidazole is stable at room temperature in solid state. The Imidazole is soluble in organic solvent DMSO, DMF, The solid imidazole products, which separated out, were filtered, washed with water and dried. The crude products, thus isolated, were pure (single spot on TLC). After completion of the reactions, solid mass was filtered and the filtrate having chitosan catalyst was reused in the next run as such without any further treatment. Recycled chitosan catalyst was reused for 15 times. Acetic acid was used in this reaction only for homogenizing the chitosan catalyst and itself did not work as catalyst which has already been studied in experiment

Table 1: Proposed Structures of Subtituted Imidazole



2-(3-chloro-4-methylphenyl)-4,5-diphenyl-1H-imidazole

Chacterization of 2-(3-chloro-4-methylphenyl)-4,5-diphenyl-1H-imidazole

Gray White Solid; $C_{22}H_{17}ClN_2$; M.P.:135^{o}C;Yield:92%; IR(KBr Cm^{-1}): 689 (C-Cl)1216,1638,2479,2878,3421,2950; ^{1}H NMR (400 MHZ.DMSO d_6) δ ppm: 2.24(s,3H), 7.32–7.50 (m,10H), 13.06 (s,1H); 7.84 (s,1H), 8.20 (d,1H), 7.16(d,1H); ^{13}C NMR($CDCl_3$/DMSO-d_6, 400 MHz) δ 19.8, ,127.4-138.2(Benzene),127.4-136.6,129.1 177.2(Imidazole); $C_{22}H_{17}ClN_2$: calcd C, 76.63; H, 4.97;N, 8.12;Found C, 75.28; H, 4.63;N, 7.89

IR Spectra of 2-(3-chloro-4-methoxyphenyl)-4,5-diphenyl-1H-imidazole s show peak at 2950 cm^{-1} is an absorption band due to C-H vibrations in the side-chain methyl group of methylbenzene ,3421Cm^{-1} for imidazole ring nitrogen atom confirms the formation of Imidazole, peak at 689 Cm^{-1} due to C-Cl stretching in imidazole ring. Also different peak at 1216,1638,2479,2878 Cm^{-1} also suggest substituted imidazole compound is formed[24].^{1}H NMR Peak at δ 2.24 for s for 3H of methyl group attached to aromatic ring, Aromatic ring peak observed in between range of δ 7.16–8.20, δ 7.32–7.50 is m,for 10H of two phenyl ring proton. δ 13.06 is for 1H attached to nitrogen atom confirms the formation of imidazole. ^{13}C-NMR spectra of imidazole show peak at δ 19.8 for methyl carbon attached to benzene ring, Aromatic carbon in benzene show peak in range between δ127.4-138.2 and imidazole ring carbon show peak in between range δ 127.4-177.2[25].Mass Spectra of Substituted imidazole shows peak at m/z 345.80 [M+H,100%], which is M+H peak at 100% intensity this peak support to the structure of the Imidazole. [26].

Antimicrobial Activity

The antibacterial screening of 2-(3-chloro-4-methylphenyl)-4,5-diphenyl-1H-imidazole revealed that Synthesized imidazole compound showed good inhibition against microbial strains tested, mainly, against S. aureus ,B.Subtlis and fungal species A. niger and F.Oxysporum compared to the reference.(Table 2)[27]

Table 2. Antimicrobial activity of Imidazole

Compounds	Antibacterial Activity		Antifungal Activity	
	S.aureus	*B.subtilis*	*A.niger*	*F.oxysporum*
	Diameter of inhibition Zone in mm	Diameter of inhibition Zone in mm	Diameter of inhibition Zone in mm	Diameter of inhibition Zone in mm
	500 ppm	500 ppm	500 ppm	500 ppm
S.Imidazole	21	26	22	20
Ciprofloxacin (Standard)	34	33	----	----
Miconazole (Standard)	----	----	31	27

IV.CONCLUSION

A general methodology of the formation of highly functionalized substituted imidazole from commonly available starting materials, in presence of catalytic amounts of Chitosan, via one-pot two component reaction is reported The salient features of this protocol are good yields, mild reaction conditions, environment friendly, superior atom economy and the readily accessibility of the catalyst. The aim of this synthesis was verifed by synthesizing substituted imidazole with the hope of discovering moieties that act as potential antibacterial, antifungal agents.

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