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Synthesis and Evaluation of Imidazole Derivatives for Antimicrobial Activity

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ABSTRACT

In the present work, a green, rapid, convenient and eco-friendly method for the synthesis of imidazoles is described. In this method, we used benzaldehyde and ammonium acetate in the presence of Chitosan catalyst, which acted as an efficient Biocatalyst. This protocol has many advantages such as short reaction time, high yield, easy separation of the catalyst. We used FT-IR, ^{1}H and ^{13}C NMR analyses were performed for the confirmation of the synthesized products. Imidazole produced good or moderate activities particularly against the tested bacteria and Fungi. Compounds displayed marked antifungal and antibacterial activity against. In the present work, a green, rapid, convenient and eco-friendly method for the synthesis of imidazoles is described. In this method, we used benzaldehyde and ammonium acetate in the presence of Chitosan catalyst, which acted as an efficient Biocatalyst. This protocol has many advantages such as short reaction time, high yield, easy separation of the catalyst. We used FT-IR, ^{1}H and ^{13}C NMR analyses were performed for the confirmation of the synthesized products. Imidazole produced good or moderate activities particularly against the tested bacteria and Fungi. Compounds displayed marked antifungal and antibacterial activity against.

Keywords : Antifungal, Catalyst, Chitosan, Imidazole

I. INTRODUCTION

Imidazoles are an important heterocyclic structural motif in functional molecules and are utilized in a diverse range of applications[1-2]Owing to the significant pharmacological or biological activities and the enormous medicinal value of imidazole-based molecules, the synthesis of the imidazole-skeleton small molecule has been paid attention to by pharmaceutical chemists and organic synthesis researchers. However, there is still a need for a simple

and efficient way to construct the imidazole heterocyclic skeleton. In recent decades, there have been numerous classical strategies for synthesizing this ring compound in the laboratory, including van Leusen imidazole synthesis [3] Debus-Radziszewski imidazole synthesis [4]Imdidazole containing drugs having important benefit in pharmaceutical industry[5] theirfore imidazole is used in different field like antiplatelet[6], antitubercular[7], antitumor[8], antiviral[9], antimicrobial[10], antiepileptic[11] Convenient Hence it is very useful in different areas due to that it is good to use Convenient method for the synthesis of imidazole [12]The synthesis of imidazoles a two bond disconnection method that has been explored by Shi and co-workers [13] used this disconnection to form trisubstituted NH-imidazoles from the reaction of benzimidateswith 2H-azirines in the presence of zinc(II) chloride.In related work, Cai and co-workers [14] showed that the addition of the anion derived from methylene isocyanides to ketenimines resulted in the formation of 1,4,5-trisubstitued imidazoles.

In some Studies Imidamides can also be used as starting materials for the synthesis of imidazoles without the need for a metal catalyst. For example,Tian et al. [15] reported the synthesis of substituted imidazole from the reaction of imidamides with sulphoxonium ylides in the presence of trifluoroacetic acid.Sundar and Rengan synthesized imidazoles from the three component reaction between benzylic alcohol, 1,2-diketone and excess ammonium acetate[16].The derivatives of 2-aminobenzimidazole, the core of the alkaloid bromoageliferin, were found to show effective antibiotic activities against multidrug-resistant bacteria, such as methicillin resistant Staphylococcus aureus and Acinetobacter baumannii[17]

Chitosan is a biodegradable, biocompatible, easy to for separation and workup, safety to use, and nontoxic, many polymers bound catalysts were recently utilized in organic synthesis.[18]

Chitosan (polysaccharide) is mostly used biopolymers in nature and from naturally occurring polysachhride Chitin we get Chitosan. The chitosan biopolymer, having amine and hydroxyl groups, provides active sites for various chemical modifications. The chitosan (CS) materials have attracted significant interest due to their remarkable properties, appropriate for physicochemical and biomedical applications. [19].Javad et al. have reported the one-pot synthesis of 1,2,4,5-tetrasubstituted imidazole derivatives by cyclic condensation of benzil, various aldehydes, aromatic amines, and ammonium acetate using nanocrystalline $MgAl_2O_4$ as a heterogeneous catalyst. [20].The synthesis of 2,3-dihydroquinazolin-4(1H)-ones, trisubstituted imidazoles, and 1,2,3-triazoles in a green medium Chitosan is used as a catalyst.[21].Chitosan is a polyelectrolyte with reactive functional groups, having gel-forming capability, with high adsorption capacity and biodegradability. Micro/nanoparticles and hydrogels are widely used in the design of chitosan-based therapeutic systems. The chemical structure and relevant biological properties of chitosan for regenerative medicine have been summarized as well as the methods for the preparation of controlled drug release devices and their application[22]Atia and Coworker synthesized 1-(2-chloroethyl) -5-methyl-2-nitro-1H-imidazole show good antibacterial activity.[23]

In the present work, we report the synthesis of 2-(3,4-dichlorophenyl)-4,5-diphenyl-1H-imidazole and their preliminary antibacterial and Antifungal profile against different bacteria and Fungi like S. aureus ,B.Subtlis and fungal species A. niger and F.Oxysporum respectively.Therefore it was interesting to study the lipophilicity of the prepared homologous compounds in relation to their antimicrobial activity.

II. METHODS AND MATERIAL

An All the chemical of analytical grade. Benzil, 3- All the chemical of analytical grade. Benzil, 3,4-dichlorobenzaldehyde, 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

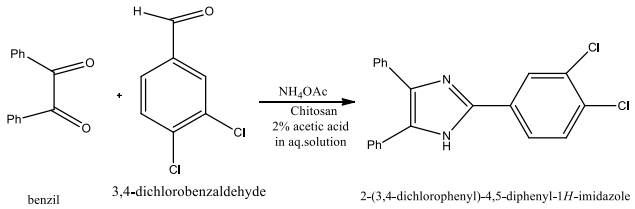
Antimicrobial Activity

2-(3,4-dichlorophenyl)-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[24].The experimental value compare with standard drug value Miconazole for the Antifungal activity and Ciprofloxacin for the antibacterial activity.

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

3,4-dichlorobenzaldehyde (0.35g, 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[25]. The reaction mixture was stirred a room temperature for 6 min. Then reaction mixture was heated at 70-75°C for 3 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

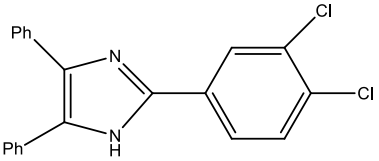


benzil 3,4-dichlorobenzaldehyde 2-(3,4-dichlorophenyl)-4,5-diphenyl-1*H*-imidazole

III.RESULTS AND DISCUSSION

2-(3,4-dichlorophenyl)-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 20 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-(3,4-dichlorophenyl)-4,5-diphenyl-1H-imidazole

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

white Solid; $C_{21}H_{14}Cl_2N_2$;132°C;Yield:92%; IR(KBr Cm^{-1}): 682,720 (C-Cl)1224,1649,2476,2888,3438; ^1H NMR (400 MHZ,DMSO d_6) δ ppm: 7.88 (s,1H), 7.45–7.58(m,10H), 8.06 (d,1H), 7.50 (d,1H),12.92 (s,1H); ^{13}C NMR($CDCl_3$/DMSO-d_6, 400 MHz) δ 126.2-136.7,126.5-173.4;$C_{21}H_{14}Cl_2N_2$: calcd C, 69.05; H, 3.86; N, 7.67 ;found C, 68.04; H, 3.23; N, 7.46;

IR Spectra of 2-(3-chloro-4-methoxyphenyl)-4,5-diphenyl-1H-imidazole show peak at 680,720 Cm^{-1} due to C-Cl bond between benzene and Chlorine and 3438 Cm^{-1} for imidazole ring nitrogen atom confirms the formation of Imidazole.Also different peak at 1224,1649,2476,2888 Cm^{-1} also suggest substituted imidazole compound is formed[26].^{1}H NMR Peak for Aromatic ring peak observed in between range of δ 7.45–7.58 is m,for 10H of two phenyl ring proton. δ 12.92 is for 1H attached to nitrogen atom confirms the formation of imidazole. ^{13}C-NMR spectra of imidazole show peak for Aromatic carbon in benzene show peak in range between 126.2-136.7 and imidazole ring carbon show peak in between range δ 126.5-173.4[27].Mass Spectra of Substituted imidazole shows peak at m/z 366.28 [M+H,100%], which is M+H peak at 100% intensity this peak support to the structure of the Imidazole. [28].

Antimicrobial Activity

2-(3,4-dichlorophenyl)-4,5-diphenyl-1H-imidazole was tested for antibacterial and antifungal activity as shown in table 2. Against different bacteria and Fungi showed extensive antifungal and antibacterial activity against S. aureus ,B.Subtlis and fungal species A. niger and F.Oxysporum Respectively[29].

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	24	28	25	18
Ciprofloxacin (Standard)	34	33	----	----
Miconazole (Standard)	----	----	31	27

IV.CONCLUSION

In summary, the low-cost, environmentally friendly catalyst, which is easily available, has advantages such as easy separation, good recycling, and remaining of the catalytic activity. Success of use Chitosan catalyst in the synthesis of functionalized imidazoles opens new avenues of their synthesis. These studies toward the improvement of catalyst materials offer new protocols for the syntheses of multisubstituted imidazoles. Although newer atom-economic approaches have evolved, there is still scope for improvement in protocols and materials for synthesis of substituted imidazole conjugates in terms of catalyst life, reactions times, and superior selectivity for future research studies and material applications. Substituted imidazole were synthesized and evaluated for their antimicrobial activity. Interestingly, the target compounds showed strong antibacterial antifungal activity.

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