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Synthesis and Antibacterial Activity of Some Imidazole-(1H) Derivatives

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ABSTRACT

There has been increased focus on the development of green and sustainable catalytic procedures for the building of novel and biologically potent imidazole conjugates. This article emphasizes the recent advances in recyclable catalysts and protocols, and their merits for the synthesis of diverse multisubstituted imidazole conjugates by one-pot reaction approach and the catalyst and reactant interactions. Imidazole, a five-membered heterocycle having three carbon atoms, and two double bonds, having efficient antibacterial activities. To search of antibacterial drugs to overcome resistance of microorganisms to antibiotics, to date hundreds of this sort of derivatives have been synthesized and possess potent antibacterial activity.

Keywords: Chitosan, Imidazole, Antibacterial, Green Catalyst.

I. INTRODUCTION

Imidazole is structurally very important molecule having diverse application.[1] Imidazoles, with nitrogen at 1 and 3 positions in the ring have been known from over 160 years. It was first reported by Henrich Debus in 1858 by reaction of glyoxal, formaldehyde, and ammonia, which afforded the low yields. [2]In recent years, the importance of imidazoles in biological systems has attracted considerable interest because of their chemical and biochemical properties, and compounds with an imidazole ring system also have many pharmacological properties and can play an important role in biochemical processes, and accordingly they have gained considerable interest among chemists. [3] Different reaction having long reaction time, low yield, acidic media, difficult work-up, expensive catalysts and excessive use of reagents and catalysts. Therefore, introducing a new green catalyst is important having good recyclability is of prime importance. [4]Literature reveals that imidazole-pyrazole hybrids containing molecules could also function as potent inhibitors of targeted enzyme. [5]

Man et al. used a related method for the synthesis of 2-aminoimidazoles Under a variety of condition,

vinylazides were converted in situ into 2H-azirines, which subsequently reacted with cyanamide to form the desired 2-aminoimidazoles in moderate to excellent yield. Both of these methods afford NH-imidazoles with control of substitution at the 2, 4 and 5 positions. [6] Yang and co-workers reported the synthesis of protected imidazoles via a $BF_3{\cdot}Et_2O$ promoted reaction of triazoles and nitriles.[7]The literature survey revealed that imidazole compounds have dynamic outcomes of versatile biological activities such as anti-cancer, [8] antiviral, [9] antifungal, [10] antibacterial, [11] anti-inflammatory, [12] antihistaminic, [13] enzyme inhibition, [14] anti-parasitic, [15] anticancer.[16]Wang and co-workers reported that the reaction of imidamides with propargyl aldehydes in the presence of a boronic acid afforded 1,2,5-substituted imidazoles. [17] A new series of novel triarylimidazoles, containing 2-arylindoles has been evaluated as inhibitors of α-Glucosidase.The synthesized compounds showed excellent inhibition activity. [18]

Alanthadka and co-workers recently built on this extensive research to develop a NHC-catalyzed protocol for the synthesis of 1,2,4-trisubstituted imidazole from the reaction of acetophenones and benzylic amines. [19]Roy and other synthesized Asymmetric synthesis of the imidazole containing b-carboline natural product, haploscleridamine, from histidine[20]Related work by Higuera et al. demonstrated that the use of the deep eutectic solvent (DES) urea/zinc(II) dichloride could catalyze the synthesis of 4,5-diphenyl-2-substituted imidazoles from the reaction of aldehydes with benzyl and excess ammonium acetate. [21] Condensation reactions to form the core four bonds of imidazoles can also be run under a variety of metal-free conditions. For example, Arafa recently reported the synthesis of tri- and tetra-substituted imidazoles over an aqueous 1, 4-diazabicyclo[2.2.2]octane (DABCO) based ionic liquid. [22] Among the many bioactive heterocyclic frameworks, nitrogen containing multi substituted imidazole heterocycles exhibit fascinating chemical behavior and activity and are versatile building blocks of many naturally occurring products with broad range of applications in diverse biological, pharmaceutical and industrial processes. [23]

Due to unique features and broad range of applications, many new imidazole derivatives have been intensively developed using different synthetic approaches.This article focuses on the exhaustive coverage of recent advances in the development and utility of Biodegradable Chitosan catalysts for the synthesis of diverse multisubstituted-imidazole conjugates through one-pot multicomponent approach, and their optimized conditions, and to identify the compatibility between the catalyst and the reactant molecules and selectivity towards product[24]Reddy et al. were able to synthesize a series of 1,2,4,5-tetrasubstituted imidazoles by using both conventional and ultrasonic irradiation by using nano c-Al_2O_3 as a reusable catalyst.[25]To the best of our knowledge, this is the I^{st} report on the application of GO–chitosan nanocomposite as a catalyst in organic reactions.Thermal stability was one of the most important factors for selecting this catalyst for this reaction. Moreover, GO–chitosan nanocomposite has good biocompatibility and biodegradability[26] Chitosan polymers are semi-synthetically derived aminopolysaccharides that have unique structures, multidimensional properties, highly sophisticated functionality and a wide range of applications in biomedical and other industrial areas [27]

New benzimidazole, benzothiazole and imidazole derivatives were synthesized by Kucukbay and other show significantly effective acivity against Enterococcus faecalis and Staphylococcus aureus. [28] Further recent literature revealed that substituted imidazoles improves the antibacterial

activity.This created interest among us to synthesize imidazole and screen them for their antimicrobial activity.

II. METHODS AND MATERIAL

All the chemical of analytical grade. Benzil, 4-methoxybenzaldehyde, 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.

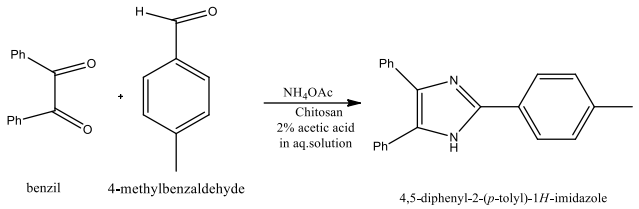
Antimicrobial Activity

4,5-diphenyl-2-(p-tolyl)-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[29].The experimental value compare with standard drug value Miconazole for the Antifungal activity and Ciprofloxacin for the antibacterial activity

Synthesis of 4,5-diphenyl-2-(p-tolyl)-1H-imidazole

4-methoxybenzaldehyde (0.27g, 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 [30]. The reaction mixture was stirred a room temperature for 5 min. Then reaction mixture was heated at 75-80^{o}C for 3.5 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).

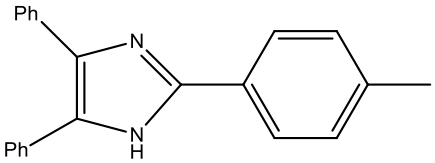
Scheme 1. Synthesis of Substitute imidazole



III.RESULTS AND DISCUSSION

4,5-diphenyl-2-(p-tolyl)-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



4,5-diphenyl-2-(p-tolyl)-1H-imidazole

Chacterization of 4,5-diphenyl-2-(p-tolyl)-1H-imidazole

White Solid; $C_{22}H_{18}N_2$;142 ^{o}C; Yield:91%; IR(KBr Cm^{-1}):1227,1648,2478,2940,3442; δ 2.30(s,3H), 7.25–7.32(d, J=8.8 Hz,2H), 7.36–7.52(m,10H),8.42–8.56(d, J= 8.8 Hz, 2H), 13.02 (s,1H); ^{13}C NMR($CDCl_3$/DMSO-d_6, 400 MHz) δ 21.4, ,127.5-138.6(Benzene),128.4-132.4,127.6 172.6(Imidazole); $C_{22}H_{18}N_2$; calcd C, 85.13; H, 5.85; N, 9.03;Found C, 84.87; H, 5.28; N, 9.27.

IR Spectra data of 4,5-diphenyl-2-(p-tolyl)-1H-imidazole show peak at 2940 Cm^{-1} is an absorption band due to C-H vibrations in the side-chain methyl group of methylbenzene. Peak at 3442 Cm^{-1} for imidazole ring nitrogen atom confirms the formation of Imidazole, Also different peak at 1227,1638,2478,2892 Cm^{-1} also suggest substituted imidazole compound is formed [31].^{1}H NMR Peak at δ 2.30 s for 3H of methyl group attached to aromatic ring, Aromatic ring peak observed in between range of δ 7.25–7.32 (d, J=8.8 Hz,2H). δ 7.36–7.52 is m,for 10H of two phenyl ring proton. δ 13.02 is for 1H attached to nitrogen atom confirms the formation of imidazole. ^{13}C-NMR spectra of imidazole show peak at δ 21.4 for methyl carbon attached to benzene ring, Aromatic carbon in benzene show peak in range between δ127.5-138.6 and imidazole ring carbon show peak in between range δ 128.4-172.6[32].Mass Spectra of Substituted imidazole shows peak at m/z 311.40 [M+H,100%], which is M+H peak at 100% intensity this peak support to the structure of the Imidazole [33].

Antimicrobial Activity

Synthesized Imidazole compound was screened for its antibacterial and antifungal activity against two micro organisms, i.e., S. Aureus, B.Subtlis and two fungi i.e., A. niger and F.Oxysporum shown in table.2 exhibited promising antibacterial activity(Table.2) [34].

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	22	26	24	19
Ciprofloxacin (Standard)	34	33	----	----
Miconazole (Standard)	----	----	31	27

IV. CONCLUSION

In summary, Chitosan has been shown to be a convenient, inexpensive, nontoxic, and recyclable Catalyst for the efficient synthesis of substituted imidazole. This protocol offers a rapid and clean alternative and reduces reaction time. It is an efficient, promising and green synthetic strategy to produce imidazole. The recyclability of the Green Catalyst makes reaction economically and potentially viable for commercial applications. During an effort to synthesize imidazoles showed appreciable antibacterial and antifungal activity.

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