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L Sarala
PG & Research Department of Chemistry, Bishop Heber College (Autonomous), Tiruchirapalli-620017, Tamil Nadu, India.

J Princy Merlin
PG & Research Department of Chemistry, Bishop Heber College (Autonomous), Tiruchirapalli-620017, Tamil Nadu, India.

I Sharmila Lydia
PG & Research Department of Chemistry, Bishop Heber College (Autonomous), Tiruchirapalli-620017, Tamil Nadu, India.

E Elanthamilan
PG & Research Department of Chemistry, Bishop Heber College (Autonomous), Tiruchirapalli-620017, Tamil Nadu, India.

Correspondence
L Sarala
PG & Research Department of Chemistry, Bishop Heber College (Autonomous), Tiruchirapalli-620017, Tamil Nadu, India.

Multicomponent reactions: An efficient and green approach to imidazole derivatives

L Sarala, J Princy Merlin, I Sharmila Lydia and E Elanthamilan

Abstract
Multi component one pot cyclo condensation reaction of tri substituted imidazole derivatives were synthesized by green route with simple, cost effective method. Characterization of the as-synthesized imidazole derivatives has been carried out by various spectral techniques such as, FT-IR spectroscopy and NMR spectroscopy. It is used to predict the structure of the molecules. The inhibition efficiency of the molecule against biological bacterial pathogens are identified with the help of Disc diffusion method.

Keywords: Imidazole derivatives, heterocyclic compounds, one pot reactions, anti-microbial activity

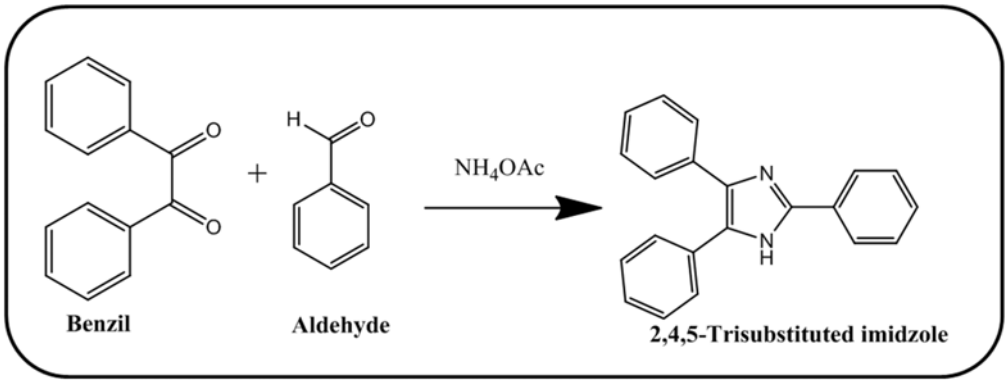
1. Introduction
In recent years, Nitrogen containing heterocyclic compounds are of current interest because of their wide applications in various fields such as pharmaceutical, cosmetics, pesticides, fungicides, disinfectant, agro chemicals, dye stuff, antifreeze, anti- inflammatory, anti-cancer, optical electronics, OLEDs and dye sensitized solar cells (DSSC), etc. [1-5]. Most of the imidazoles core structures has present in many biological systems like histidine, histamine and biotin. Notably tri aryl imidazoles are used in photography as photo sensitive compounds. [6-8]. As a result the role of imidazoles is noteworthy in the field of organic chemistry. The synthesis and characterization of trisubstituted imidazole that are used to satisfy the current requirements is one of the important research topics.
Literature scanning clearly reveals that the number of divergent methods for the synthesis of tri substituted imidazoles. In general, synthesis comprises the condensation of a diketone, an aldehyde and ammonium acetate. It was first suggested by Radsziszewki in 1882, though this method has lot of potential, some of the reported variants were not applied for the synthesis of structurally diverse imidazoles.
Owing to its wide applicability in industry and laboratory, the hunt for efficient synthesis increases. Modification of the synthetic procedure like varying the synthetic routes namely, reflux, microwave, sonochemical etc., and by altering the solvents such as acetic acid, silica supported sulphuric acid, ionic liquids, etc., were carried out to improve the yield. In addition the modification of the catalyst like $InCl_3.H_2O$, ceric ammonium nitrate, $NiCl_2$. $6H_2O/Al_2O_3$, L-proline, $ZrCl_4$, ZnO and Silica supported metal oxide, etc [9, 10]. Every procedure has its own merits and drawbacks. Therefore the development of new synthetic protocol under solvent free, catalyst free green route at ambient conditions for tri substituted imidazoles is anticipated in the present study.

2. Experimental Methods
2.1 Materials and Methods
Chemical reagents such as diketone, substituted benzaldehydes and ammonium acetate were purchased from sigma Aldrich and used without further purification. Solvents such as ethanol, acetone, methanol and diethyl ether are of analytical grade. Elemental analysis was carried out using Perkin-Elmer, 240 elemental analyser. Infrared spectra were recorded on a Perkin- Elmer FT-IR spectrometer in the range of 4000-400 cm^{-1} using KBr pellets. ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 (99.95% atom% D, Aldrich) on a Bruker WP 400 MHz spectrometers. Chemical shifts (δ) are expressed in ppm downfield from tetramethylsilane using the residual protonated solvent as an internal standard.

Coupling constants are expressed in hertz. Antimicrobial susceptibility test is carried out using disc diffusion technique.

2.2 Synthesis of tri-substituted imidazole derivatives

A sample of Benzil, substituted benzaldehydes and ammonium acetate were mixed in 50 ml round-bottom flask, in the ratio of 1:1:3, and this mixture was refluxed for 6 h at 140 ºC. The progress of the reaction was monitored by TLC using Toluene: Ethyl acetate (7:3) eluent. The reaction mixture was cooled and washed three times with hot water. The solution was brought to dryness and then was washed with methanol. The solid was dried under vaccum to give a required product.



Scheme 1: Schematic representation of synthesis of Tri-substituted imidazoles

The aromatic aldehydes used for the present synthesis of imidazoles are varied to get different tri-substituted imidazole derivatives, the aldehydes used in the present work are as follows.

Table 1: List of aldehydes used in the above scheme

S. No	Aldehydes	Name of the synthesized compound	Molecular formula
1	Benzaldehyde	2,4,5-triphenyl-1H-imidazole - (TPI-1)	$C_{21}H_{16}N_2$
2	2-hydroxybenzaldehyde	2-(4,5-diphenyl-1H-imidazol-2-yl)phenol - (TPI-2)	$C_{21}H_{16}N_2O$
3	4-hydroxybenzaldehyde	4-(4,5-diphenyl-1H-imidazol-2-yl)phenol - (TPI-3)	$C_{21}H_{16}N_2O$
4	3,4-dihydroxybenzaldehyde	4-(4,5-diphenyl-1H-imidazol-2-yl)benzene-1,2-diol - (TPI-4)	$C_{21}H_{16}N_2O_2$
5	2,4-dimethoxybenzaldehyde	2-(2,3-dimethoxyphenyl)-4,5-diphenyl-1H-imidazole - (TPI-5)	$C_{23}H_{20}N_2O_2$

2.3. Results and discussion

Elemental analysis and the melting point obtained for the as synthesized compounds are listed in the (Table.2). The elemental analysis calculated was found to be in good agreement with the obtained value

Table 2: Yield and Elemental Analysis Data of the Synthesized Compound

S. No	Compound Name	Yield (%)	Elemental analysis							
			Calculated				Found			
			C	H	N	O	C	H	N	O
1	TPI-1	85	85.11	5.44	9.45	--	85.45	5.12	9.36	--
2	TPI-2	80	80.75	5.16	8.97	5.12	81.01	5.21	8.71	5.45
3	TPI-3	82	80.75	5.16	8.97	5.12	80.12	5.47	8.54	5.08
4	TPI-4	74	76.81	4.91	8.53	9.74	76.14	4.58	8.11	9.87
5	TPI-5	78	77.51	5.66	7.86	8.98	77.39	5.91	7.24	8.23

2.3.1 Vibrational spectroscopy

FT-IR spectroscopy is used to find out the presence of functional group. A strong absorption band around 1634 cm^{-1} and 3475 cm^{-1} for all the synthesized compounds in FT-IR confirms the presence of C=N and N-H stretching, in addition weak bending at 1400cm^{-1} indicates the presence of aromatic C=C. In Particular, a broad peak around 3300cm^{-1} is obtained shows the existence O-H stretching in TPI-2, TPI-3 and TPI-4 respectively.

2.3.2 NMR spectroscopy

The ^1H NMR spectral analysis of the as synthesized compounds showed a characteristic peak at δ 12.85 ppm clearly indicates the presence of N-H proton, the presence of aromatic protons in all the compounds is clearly identified by the chemical shift value at 7.45ppm, in addition the presence of hydroxyl proton in the compounds TPI-2, TPI-3 and TPI-4 is verified by the obtained chemical shift value at 5.12 ppm, 5.23 ppm, 5.46 ppm respectively. The methoxy proton in the TPI-5 derivative is confirmed by the δ value at 3.74 ppm. The ^{13}C NMR spectroscopy were examined in order to predict the structure of the as synthesized imidazoles. The characteristic C=N group in all the compounds shows different chemical shift for every compound because of the different chemical environment, in the case of TPI-1, TPI-3 and TPI-4 it shows δ value at 177 ppm but for TPI-2 and TPI- 4 it was found to be 147 ppm due to the presence of adjacent hydroxyl and methoxy group respectively. It was in good agreement with the literature. The δ value at 149 ppm, 154 ppm, 152 ppm and 165 ppm

shows the existence of C-O group in TPI-2, TPI-3, TPI-4 and TPI-5. In addition the medium peak for TPI-5 at 62 ppm is attributed to the presence of methoxy carbon. From the above discussion the proposed structure of the synthesized imidazole are shown below.

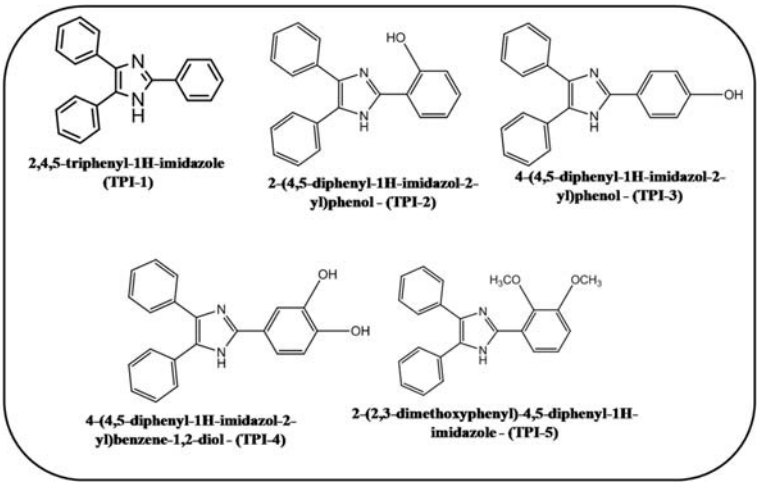


Fig 1: Plausible Structure of the synthesized imidazole derivatives

2.3.3 Antimicrobial activity

The synthesized compounds TPI-1, TPI-2, TPI-3, TPI-4 and TPI-5 with standard control were tested against antimicrobial activity. The precursor TPI-1 and TPI-4 possess nearly equal to antimicrobial activity and newly synthesized compounds TPI-(1-5) enhance the antimicrobial to a greater extent. Especially TPI-1 and TPI-4 possess high antibacterial activity. The standard control used for antibacterial were ciprofloxacin.

2.3.3.1 Antibacterial activity (Protocol)

Antibacterial assay was done by disc diffusion method. The media Mueller Hinton agar was prepared for antibacterial activity. The concentration of the given samples (5µg/disc) was applied on the sterile discs. 25µl of each sample was added to the sterile discs and placed on the agar plate. Ciprofloxacin was used as an antibacterial agent for the control. The incubation was carried out at 37 ^{0}C for 24 h. The diameters of the inhibition zones were measured in mm.

Table 3: Results of antimicrobial studies using the synthesized imidazoles

S. No.	Name of the microorganisms	Zone of inhibition in diameter					Standard Ciprofloxacin 5µg/disc (mm)
		TPI-1	TPI-2	TPI-3	TPI-4	TPI-5	
1	E. coli	21	20	20	19	19	22
2	P. aeruginosa	14	15	16	14	15	16
3	S. aureus	15	14	12	16	12	17
4	P. vulgaris	17	17	15	17	18	19
5	S. pneumonia	16	15	12	18	14	20
6	E. sps	15	17	13	19	16	21

The following graph shows the inhibitive effect of the synthesized imidazole and standard one towards various microorganisms.

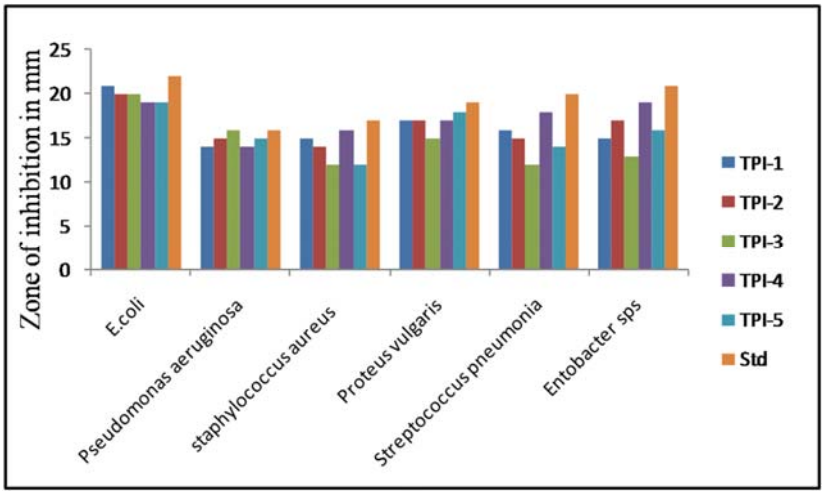


Fig 2: Zone of inhibition towards the microorganisms using synthesized imidazoles

3. Conclusion

In the present work, we have developed the green ecofriendly synthesis of substituted imidazoles were synthesized successfully, the synthesized imidazole derivatives were characterized by IR to examine the presence of required functional group. In addition, NMR spectroscopy results also reveals the structure of the molecules from its appropriate chemical shift values. The experimental results were found to be in good agreement with the reported literatures. The antimicrobial activities of the imidazole derivatives were tested for all compounds showed moderate antibacterial activity. Antibacterial activity of TPI-1 and TPI-4 with standard control ciprofloxacin against E. coli and S. aureus shows a high activity against bacterial strains.

4. Acknowledgement

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