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An Efficient Synthesis of 2, 4, 5-Triphenyl Imidazole Derivatives Promoted By Mg $(NO_3)_2$

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ABSTRACT:

A simple, highly versatile and an efficient synthesis of 2, 4, 5-trisubstituted imidazole that was obtained by three component cyclocondensation of benzil, substituted aromatic aldehydes and ammonium acetate in solvent free condition using Mg $(NO_3)_2$ acts as catalyst. The main advantages of this method of process are cost effectiveness of catalyst, easy work-up and purification of products by non-chromatographic methods, good to excellent yields and very short reaction time. The newly synthesized derivatives were evaluated by advanced spectroscopic data such as ^{1}HNMR, ^{13}CNMR and LCMS and the structural determination of the desired compounds were determined by elemental analysis.

Keywords:

2, 4, 5 -Triaryl imidazole, benzil, substituted aromatic aldehydes, Ammonium acetate, Mg $(NO_3)_2$

1. INTRODUCTION:

There is an urgent need to create new kinds of antibacterial medications, particularly ones that can overcome drug resistance and/or have a new pharmacological target. The longevity of antifungal agents like azoles, antiviral agents like no nucleoside reverse transcriptase inhibitors [5], and different antibacterial agents like imidazole and benzimidazole (1–5) can be effectively extended by structurally altering antimicrobial medications to which resistance has developed.

In recent time, Nitrogen containing heterocyclic compounds is highly interest because of their various applications in different fields such as pharmaceutical, cosmetics, pesticides, fungicides, disinfectant, agro chemicals, dye stuff, antifreeze, anti- inflammatory, anticancer, optical electronics, OLEDs and dye sensitized solar cells (DSSC), etc. (6-10). Imidazole is five membered heterocyclic compounds that contain two nitrogen atoms at position “1”and “3” and also it was under intensive focus mainly due to their broad range of applications in organic synthesis and medicinally chemistry. The study of synthesis of imidazole moiety is very significant play a role due to their potent biological activity and synthetic utility. Imidazole is the most important class of heterocyclic compounds which have been developed the core fragment of various natural products and biological systems. Most of the imidazole’s core structures has present in many biological systems like histidine, histamine and biotin. Notably tri aryl imidazole’s are used in photography as photo sensitive compounds. (11-13). Compounds possess imidazole moiety which have many pharmacological properties and also play an important role in biochemical processes. The potent activity and wide applicability of the imidazole pharmacophores can be attributed to its hydrogen bond donor-acceptor capability as well as its high affinity for metals, which are present in many proteins’ active sites. Naturally occurring substituted imidazole and its synthetic derivatives exhibit wide ranges of biological properties, making them attractive compounds for organic chemists 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.

2. METHODS AND MATERIALS

2.1. GENERAL

All reagents, chemicals and solvents were procured from Sigma Aldrich and Merck chemicals and they are used without further purification. The melting points of the synthesized compounds were measured by an instrument Agarwal thermo meter open capillary method using a Galen Kamp melting point apparatus and are uncorrected. The required Products were analysed by spectroscopy data (^{1}HNMR and ^{13}CNMRspectra and LCMS) Bruker spectrometer. NMR spectra were measured on a Bruker Avance (400-MHz) NMR and $CDCl_3$ was used as a solvent. The purity of the substances and the progress of the reactions were checked on TLC.

2.2. General Methods for Synthesis of 2,4,5- Trisubstituted Imidazole:

Taken clean and dry 20mL rounded bottom flask arranged on the magnetic stirrer. The mixture of benzil (1mol), substituted aromatic aldehydes (1.125mol), and ammonium acetate (2.5mol) were introduced in a RBF and the appropriate amount catalyst such as Mg $(NO_3)_2$ was added (3mmol). Then the reaction mixture was continued to reflux for the appropriated time of period. After completion of the reaction which was checked by TLC as mobile phase (5:5-EtOAc: n-hexane), the mixture taken in an ethyl acetate and washed with water, the solid product can be separated and purified by recrystallization from ethanol.

Spectral and Analytical Data

2.2.1. 2, 4, 5-Triphenyl-1H-imidazole (4a).

Yellowsolid;M.p-187-189^{0}C;Yield-80%:^{1}HNMR(400MHz,$CDCl_3$)ppm:11.142(s,1H,NH-imidazole), 8.210-8.029(m,2H,Ar-H),7.857-7.289(m,13H,Ar-H);^{13}CNMR(100MHz,$CDCl_3$)ppm:149.78,139.45, 136.56,132.25,130.06,129.57,128.78,128.22,127.88,127.32,125.91;LCMS(m/z):297.54(M+H); Molecular formulae: $C_{21}H_{16}N_2$; Elemental analysis : Calculated: C-85.10,H-5.43 ,N-9.44 , Obtained : C- 85.03 ,H-5.41 , N-9.47. .

2.2.2. 4-(4, 5-Diphenyl-1H-imidazol-2-yl)-phenol (4b):

Paleyellowsolid;.Mp-231–233°C.Yield-88%;^{1}HNMR(400MHz,$CDCl_3$):11.327(s,1H,-NH-imidazole), 9.654(s,1H,OH),7.793-7.655(m,2H,Ar-H),7.619–7.287(m,10H,Ar-H),7.204-7.045(m,2H,Ar-H); ^{13}CNMR(100MHz,$CDCl_3$):158.07,149.12,138.25,132.64,130.08,129.31,128.52,127.21,125.85,123 .66,120.09,116.77,113.81,98.66,95.48.38;LCMS(m/z):313.87(M+H); Molecular formulae: $C_{21}H_{16}N_{2O}$; Elemental analysis: Calculated: C-80.75, H-5.16, N-8.97, Obtained: C- 80.67 , H-5.15 , N-9.05

2.2.3.4-(4, 5-diphenyl-H-imidazol-2-yl)-2-hydroxy phenyl acetate (4c):

Pale-yellow;Mp-241–242°C.Yield-90%;^{1}HNMR(400MHz,$CDCl_3$):11.296(s,1H,-NH-imidazole), 9.31 4(s,1H,OH),7.741–7.285(m,12H,Ar-H),7.224(s,1H,Ar-H),1.886(s,3H,-OCOCH$_3$);^{13}CNMR(100 MHz, $CDCl_3$):164.17,143.54,141.65,137.77,129.88,128.54,128.12,127.75,125.08,122.77,118.27,115.55, 60.32;LCMS(m/z):370.57(M+);Molecularformulae:$C_{23}H_{18}N_2O_3$.Elementalanalysis:Calculated:C-74.58,H-4.90,N-7.56:Obtained:C-74.52 ,H-4.89 ,N-7.65.

2.2.4. 2-(4-Methoxyphenyl)-4,5-diphenylimidazole (4d):

Paleyellowsolid;Mp.254-256°C.Yield-91%,;^{1}HNMR(400MHz,$CDCl_3$):11.257(s,1H,-NH-imidazole), 8.174-8.054(m,2H,Ar-H),7.607-7.286(m,10H,Ar-H),7.157-7.109(m,2H,Ar-H),3.751(s,3H,OCH$_3$) ;^{13}CNMR(100MHz,$CDCl_3$)ppm:159.98,147.79,137.25,135.12,131.35,130.07,128.14,127.51,124,40,

112.71,55.06;LCMS(m/z):327.12(M+H);Molecularformulae:$C_{22}H_{18}N_2O$.Elementalanalysis: Calculated: C-80.95, H-5.55, N-8.57, Obtained: C-80.88, H-5.54, N-8.650.

2.2.5.2-(2,4,6-trimethoxyphenyl)-4,5-diphenylimidazole (4e):

White compound: Mp-254–256°C.^{1}HNMR(400MHz,$CDCl_3$): 11.453 (s, 1H, -NH), 7.874 (d, J=7.8 Hz,2H,Ar-H),7.675–7.299(m,10H,Ar-H),6.962(d,J=7.6Hz,2H,Ar-H),3.705(s,6H,-OCH_3),3.678(s,3H,-OCH_3);^{13}CNMR(100MHz,$CDCl_3$):157.64,146.36,128.92,127.07,124.62,122.95,115.71,112.84, 99.25, 96.48;LCMS(m/z):386.36(M+);Molecularformulae:$C_{24}H_{22}N_2O_3$Elemental analysis: Calculated: C-74.55, H-5.74, N-7.25, Obtained- 74.46, H-5.73, N-7.33

2.2.6. 4-(4,5-diphenyl-1H-imidazol-2-yl)-N,N-diethyl aniline(4f):

PaleYellowcompound;Mp-257-259°C.;1HNMR(400MHz,$CDCl_3$):11.555(s,1H,NH-imidazole), 7.774 -7.585(m,2H,Ar-H),7.552-7.281(m,10H,Ar-H),7.198-7.012(m,2H,Ar-H);3.324-3.054(m2H,Ar-H), 1.124(t,j=8.0Hz,3H,CH_3),^{13}CNMR(400MHz,$CDCl_3$)ppm:163.77,143.95,137.17,129.55,128.60,128. 07,127.51,119.77,115.72,47.39,13.54;LCMS(m/z):368.58(M+H);Molecularformulae:$C_{25}H_{25}N_3$. Elementalanalysis: Calculated:C-81.37,H-6.23,N-12.37 :Obtained : C-81.30,H-6.21 ,N-12.44.

2.2.7. 2-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazole (4g):

Yellow compound ; Mp-258-260°C.^{1}HNMR (400MHz, $CDCl_3$) ppm: 11.475 (S. 1H, NH-imidazole), 8.184 (d, J=8.0 Hz, 2H, Ar-H), 7.812-7.326 (m, 12H, Ar-H); ^{13}CNMR(100 MHz, $CDCl_3$):148.42,137.29,135.65,131.71, 130.09, 129.26, 128.94, 128.59, 128.32,128.21,128.04, 127.77, 127.17, 126.84, 126.47; LCMS (m/z):332.54(M+2);Molecular formulae: $C_{21}H_{15}ClN_2$. Elemental analysis: Calculated: C-76.25,H-4.57 ,N-8.47,Obtained: C- 76.17 ,H-4.55 , N-8.55 .

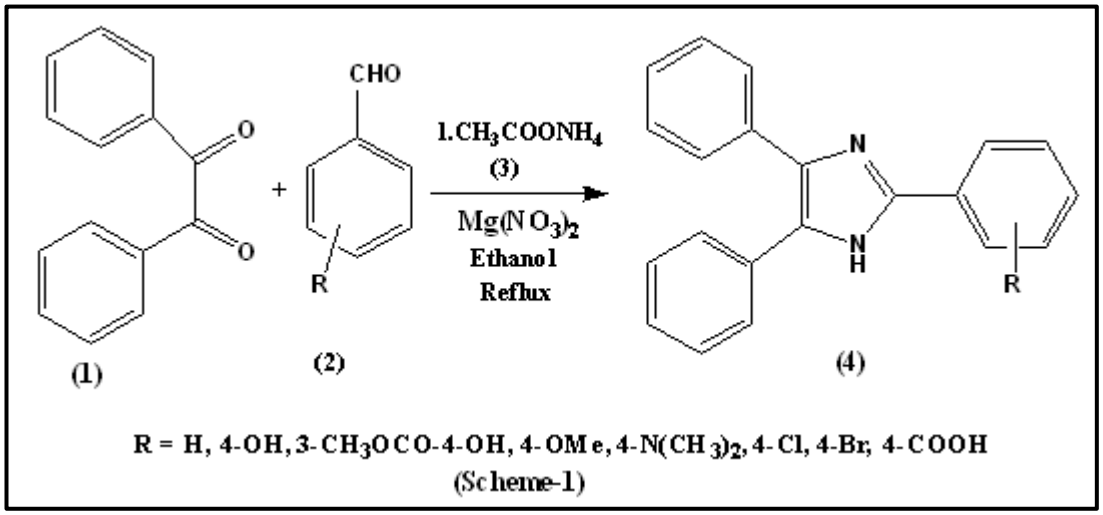
2.2.8. 2-(4-Bromophenyl)-4,5-diphenyl-1H-imidazole (4h):

Red compound; Mp-264-266°C;^{1}HNMR (400MHz, $CDCl_3$)ppm:11.248(s,1H,NH-imidazole),8.204(d, J=8.2Hz,2H,Ar-H),7.774-7.285(m,11H, Ar-H),^{13}CNMR(100MHz,$CDCl_3$):180.41,139.55,137.17,132. 67,131.71,129.61,128.90,128.54,128.47,127.84,127.50,127.14,126.78,126.32:LCMS(m/z):375.87(M+2): Molecularformule: C21H15BrN2.Elementalanalysis: Calculated: C-67.21,H-4.0 ,N-7.47 ,Obtained : C- 67.15,H-4.02, N- 7.55 .

2.2.9. 4-(4,5-diphenyl-1H-imidazol-2-yl) benzoic acid (4i):

PaleredMp-259-261°C ;^{1}HNMR(400MHz,$CDCl_3$):11.667(s,1H,NH-imidazloe),8.310-8.015(m,2H,Ar-H),7.948-7.794(m,2H,Ar-H),7.722-7.318(m,10H,Ar-H);^{13}CNMR(100MHz,$CDCl_3$):169.06,158.75, 155.52,145.62,137.41,134.47,132.87,132.24,129.87,129.54,129.21,129.02,128.92,128.47,128.11, 127. 85,127.41,127.21,126.76,126.38,126.04,124.66;LCMS(m/z):341.31(M+H);Molecularformulae: $C_{22}H_{16}N_2O_2$; ElementalAnalaysis: Calculated: C-77.64 ,H- 4.73 ,N-8.24, Obtained : C- 77.58,H- 4.72, N- 8.34.

3.1. RESULTS AND DISCUSSION:



(Scheme-1)

In continuation of our research work on the use of simple inorganic non-toxic catalysts, we report herein the efficacy of methane sulphonic acid as catalyst as well as solvent. In this study the multicomponent reaction strategy for the preparation of 2, 4, 5-triaryl-1H-imidazole by using benzil, various substituted aldehydes and ammonium acetate in presence of methane sulphonic acid as catalyst, in ethanol at reflux condition is introduced.

In a model reaction, the mixture of substituted aryl aldehyde (1.125mol), benzil (.1251mol) and NH_4OAc (2.5mol) as ammonia source, in the presence of magnesium nitrate as a catalyst was stirred at reflux under solvent conditions and the 2, 4, 5-triphenyl imidazole are obtained in 92% yield and different kinds of functional groups bearing benzaldehyde were also subjected in the presence of magnesium nitrate at Reflux ethanol as solvent conditions (Table-1)

We observed that for aldehydes having either electron withdrawing or electron-releasing groups as a substituent in the para positions; the reaction proceeded very efficiently in all cases. This method provides trisubstituted Imidazoles directly, in relatively reaction times is very short, high yields. Furthermore, we used benzoin instead of benzil and in this case corresponding products were achieved in good yields. In all cases, complete conversion was observed after appropriate time and the products were readily isolated in very high yields.

Table-I: The various catalysts applied during the synthesis:

S.NO	catalyst	Solvent	Time (hrs.)	Yield (%)
1	$FeCl_3$	Ethanol	10	71
2	TiO_2	Ethanol	12	59
3	$ZrOCl_2$	Ethanol	07	66
4	$Mg(NO_3)_2$.	Ethanol	03	94

Hence, the various lews acid catalysts applied above synthesis. But all the catalyst used to perform as the catalysts during this condition. Mg $(NO_3)_2$ was performed as a catalyst and in ethanol solvent. The advantages of this catalyst such as obtained excellent yield, easy to workup, as well as fast rate of reaction with low time bound. It is available commercially, cost effectiveness compared to other catalyst showed table above.

NMR spectroscopy:

The 1H NMR spectral analysis of the as synthesized compounds showed a characteristic peak at δ 11.478-10.474 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 8.354-7.052, in addition the presence of hydroxyl proton in the

compounds 4b, 4cshowed 9.564 and 9. 167.verified by the obtained chemical shift value at 3.596ppm respectively. The methoxy proton in the 4d, 4e derivatives are confirmed by the δ value at 3.678 ppm and 3.696, 3.587. The ^{13}C NMR spectroscopies were examined in order to predict the structure of the as synthesized imidazoles. It was in good agreement with the literature. The δ value at 142 ppm, 149 ppm, 151 ppm and 164 ppm are obtained. The molecular weight of the titled compounds was obtained (M+2), (M+H) and M^+ respectively.

3.2. Antimicrobial activity:

Antibacterial activity

Preliminary investigation of anti-microbial activity of newly synthesized compounds (4a-4h) was evaluated by cup plate method. We used different pathogenic strains viz. Staphylococcus aureus, B-substills (gram positive), P.aeruginose, S.typhi, and E.coli (gram negative) using standard drug Streptomycin for antibacterial growth.

Nutrient agar medium (NAM) is used to test for the anti-bacterial activity of titled compounds; NAM was prepared with beef extract (4g), peptone (7g), NaCl (5g) agar (20g) en 1000 ml distilled water and PH was maintained to 7.1. NMA was sterilized in an auto clave at 121℃ 15 lbs pressure for 45 min. After sterilization, 20 ml of NAM was poured into petro dishas in a laminar air flow and allowed to solidity. After solidification, NMA was in occulated with 100 µl of derived bacteria. The tested derivatives were dissolved in DMSO with a concentration of 100 ppm, 250 ppm and whatsman No.1 filter paper disks were placed in the solution and kept for one minute. After drying the disks were placed as NAM inoculated with bacteria and NAM plates were incubated at 37 ℃. Zones of inhibition were measured after 24 hrs. Compared with **Streptomycin.**

S.NO	Compound	Gram Negative						Gram Positive			
		P.aeruginose		S.typhi		E.coli		S.aureus		B.substill	
		250	500	250	500	250	500	250	500	250	500
1	4a	06	09	05	13	04	11	02	05	04	08
2	4b	11	15	10	17	09	15	11	18	08	14
3	4c	06	12	09	15	11	17	11	15	08	15
4	4d	11	16	10	16	11	18	09	16	09	12
5	4e	08	14	9	15	8	14	07	13	08	15
6	4f	06	13	07	15	08	16	07	12	08	12
7	**4g**	**11**	**18**	**12**	**18**	**08**	**16**	**10**	**18**	**09**	**18**
8	**4h**	**11**	**18**	**10**	**18**	**08**	**17**	**10**	**17**	**08**	**18**
9	4i	04	06	07	08	05	09	04	09	05	09

	Streptomycin	20	20	20	20	22	22	22	22	20	20
	DMSO	-	-	-	-	-	-	-	-	-	-

The compound '4a&4i' exhibited poor active potential due to aryl substituent containing electron with dragging groups whereas compounds such as '4f' showed moderate active potential containing electron donating groups. Other hand, the compounds 4b, 4d , 4e having good active potential due to highly electron donating groups. From the above table, we observed that the compound "4g and 4h "exhibited good active potential.

4.2. CONCLUSION:

Multicomponent reactions enjoy an outstanding status in organic and medicinal chemistry for their high degree of atom economy and application in the diversity-oriented convergent synthesis of complex organic molecules from simple and readily available substrates in a single vessel. A simple highly versatile and efficient synthesis of 2,4,5-trisubstituted imidazole is achieved by three component cyclocondensation of 1,2-dicarbonyl compounds, aldehydes and ammonium acetate as ammonia source in thermal solvent condition using Mg $(NO_3)_2$ as catalyst. The key advantages of this process are cost effectiveness of catalyst, reusability of catalyst, easy work-up and purification of products by no chromatographic methods, excellent yields and very short time reaction. In additionally, the compounds showed satisfactorily antibacterial activity.

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6. REFERENCES:

[1] Valls, A., Andreu, J.J., Falomir, E., Santiago, V.L., Atrián-Blasco, E., et al. **(2020)**

Imidazole and Imidazolium Antibacterial Drugs Derived from Amino Acids. Pharmaceuticals, 13, 482. https://doi.org/10.3390/ph13120482

[2] Liu, C., Shi, C., Mao, F., Xu, Y., Liu, J., et al. **(2014)** Discovery of New Imidazole Derivatives Containing the 2,4-Dienone Motif with Broad-Spectrum Antifungal andAntibacterialActivity.Molecules,19,15653-15672. https://doi.org/10.3390/molecules191015653

[3] Salahuddin, Shaharyar, M. and Mazumder, A. **(2017)** Benzimidazoles: A Biologically Active Compounds. Arabian Journal of Chemistry, 10, S157-S173.https://doi.org/10.1016/j.arabjc.2012.07.017

[4] Sharma. S., Sharma, V., Singh, G., Kaur, H., Srivastava, S. and Ishar, M.P.S. **(2017)**

2-(chromon-3-yl) Imidazole Derivatives as Potential Antimicrobial Agents: Synthesis, Biological Evaluation and Molecular Docking Studies. Journal of Chemical Biology, 10, 35-44. https://doi.org/10.1007/s12154-016-0162-8

[5] Tahlan, S., Kumar, S. and Narasimhan, B**. (2019)** Antimicrobial Potential of1H-Benzo[d] Imidazole Scaffold: A Review. BMC Chemistry, 13, Article No. 18.https://doi.org/10.1186/s13065-019-0521-y.Journal of the Chemical Society (Resumed), 2393-2399.

[6]. Sadeghi B. SbCl5. SiO2: an efficient alternative for onepot synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles insolvent or under solvent-free condition. Journal of the Iranian Chemical Society. 2011; 8(3):648-652.

[7]. Wang, Liang, Chun Cai. Polymer-supported zinc chloride: a highly active and reusable heterogeneous catalyst for one-pot synthesis of 2, 4, 5-trisubstitutedimidazoles. Monatshefte für Chemie-Chemical Monthly. 2009; 140(5):541-546.

[8]. Bahrami, Kiumars, Mohammad M. Khodaei, and Akbar Nejati. One-pot synthesis of 1, 2, 4, 5-tetrasubstituted and 2, 4, 5-trisubstituted imidazoles by zinc oxide as efficient and reusable catalyst. Monatshefte fürChemieChemical monthly. 2011; 142(2):159-162.

[9]. Das Biswanath. Synthesis of 2, 4, 5-trisubstituted and 1, 2, 4, 5-tetrasubstituted imidazoles in water using pdodecylbenzenesulfonic acid as catalyst. Monatshefte further Chemie-Chemical Monthly. 2013; 144(2):223-226.

[10]. Khaksar Samad, Mandana Alipour. Lewis acid catalyst free synthesis of substituted imidazoles in 2, 2, 2-trifluoroethanol. Monatsheftefür Chemie-Chemical Monthly. 2013; 144(3):395-398.

[11].Липунова ГН, Носова ЭВ, Чарушин ВН. Fluoro imidazoles and Their HeteroannulatedDerivatives: Synthesis and Properties. Chemistry of Heterocyclic Compounds. 2013; 12:1825-1851.

[12]. Gelens E. Efficient library synthesis of imidazoles using a multicomponent reaction and microwave irradiation. Molecular diversity. 2006; 10(1):17-22.

[13]. Karimi Ali Reza, Zahra Alimohammadi, Mostafa M. Amini. Wells-Dawson heteropolyacid supported on silica: a highly efficient catalyst for synthesis of 2, 4, 5-trisubstituted and 1, 2, 4, 5-tetrasubstituted imidazoles. Molecular diversity. 2010; 14(4):635-641.