International Journal of Scientific Research in Engineering and Management (IJSREM)
Volume: 09 Issue: 04 | April - 2025 SJIF Rating: 8.586 ISSN: 2582-3930

Multicomponent Synthesis Of 2, 4, 5-Triphenyl Imidazole Derivatives by Grinding Method

P. Varaprasad[1], B.Manish Patnaik[1], Dr.N.Krishnarao rao[1*]

1*.Department of Organic chemistry, PRISM PG&DG College, (Andhra University), Visakhapatnam, India

Corresponding Author-Email ID: naallakrishnarao@gmail.com

ABSTRACT :

An efficient synthesis of 2,4,5-trisubstituted imidazoles is prepared by three component cyclocondensation of 1,2-dicarbonyl compounds, substituted aryl aldehydes and ammonium acetate in presence of PTSA as catalyst followed by grinding method . All the derivatives were analysed by advanced spectroscopic data viz; ^{1}H NMR, ^{13}C NMR and LCMS and the structure of the molecule determination of the derivations was calculated by elemental analysis. The scope and advantages this process is cost effectiveness of catalyst, easy work-up and purification of products by non-chromatographic methods, good to excellent yields and very short time reactions and The compounds are evaluated for their *invitro* anti-bacterial activity

KEYWORDS:

2, 4, 5-triarylimidazoles, benzil, aromatic aldehydes, PTSA, Grinding method, Antibacterial activity

1. INTRODUCTION

Imidazoles are a class of heterocyclic compounds that contain nitrogen atom and are currently under intensive focus due to their wide range of applications [1]. Synthetic study of imidazole units is very important due to their potent biological activity [2] and synthetic utility [3]. Imidazoles are an important class of heterocycles being the core fragment of different natural products and biological systems. Compounds containing imidazole moiety have many pharmacological properties and play important roles in bio chemical processes [4]. The potency and wide applicability of the imidazole pharama cophores can be attributed to its hydrogen bond donor-acceptor capability as well as its high affinity for metals, which are present in many protein active sites [5,6].

Naturally available substituted imidazoles as well as synthetic derivatives thereof, exhibit broad range ranges of biological properties and making them attractive derivatives for organic synthesis. They act as inhibitors of p38 MAP kinase [7], B-Raf kinase [8], transforming growth factor b1 (TGF-b1) type 1 active in receptor-like kinase (ALK5)[9], cyclooxygenase-2 (COX-2) [10] and biosynthesis of interleukin-1 (IL-1) [11]. Appropriately substituted imidazoles are extensively used as glucagon receptors [12] and CB1 cannabinoid receptor antagonists [13], modulators of P-glycoprotein (P-gp)-mediated multidrug resistance (MDR) [14], antibacterial and antitumor agents [15] and also as pesticides [16]. Recent advances in green chemistry and organometallic catalysis has extended the application of imidazoles as ionic liquids [17] and Nheterocyclic carbenes [18].Ionic liquid (IL) technology offers a new and environmentally benign approach toward modern synthetic chemistry. Ionic liquids have interesting advantages such as extremely low vapour pressure, excellent thermal stability, reusability, and talent to dissolve many organic and inorganic substrates. Ionic liquids have been successfully employed as solvents and catalyst for a variety of reactions which promise widespread applications in industry and organic syntheses [19].

We report here a simple and efficient producers for the preparation of the 2, 4, 5-triarylimidazoles promoted by grinding method in the presence of PTSA acidic as catalyst that is considered as efficient catalyst. The methodology reported here in, the represents a good addition to the list of methods available for the synthesis of highly substituted imidazoles derivatives.

2. Methods and Materials:

2.1. Experimental.

All reagents, chemicals and solvents were commercially purchased from Aldrich and Merck and used without further purification. The newly synthesized derivatives of melting points that determined by open capillary method using a Galen Kamp melting point apparatus and is uncorrected. The titled products were characterized by spectroscopy data ^{1}H NMR, ^{13}C NMR and LCMS and melting points. NMR spectra were recorded by the compounds on a Bruker (400-MHz) Ultrasheild NMR and $CDCl_3$ was used as a solvent. The purity of the compounds and the progress of the reactions were monitored by use of TLC.

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

The mixture of Benzil (1mol), aldehyde (1mol), and ammonium acetate (2mol) were charged into in clean and dry mortar and Bronsted acid catalyst such as PTSA added in a above the mixture . The mixture was grinded with use of pestle as in Scheme-I. Then the powder was neutralised with saturated $NaHCO_3$ solution. After completion of the reaction, progress grinded of the reaction was checked by TLC, the mixture was cooled, poured in crushed ice and also neutralised with sodium carbonate solution. The mixture was extracted with ethyl acetate and washed with water. The ethyl acetate layer was separated followed by distillation U/vacuumed and the solid product purified by recrystallization from ethanol.

Spectral and Analytical Data:

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

Palered**;** M.p. 214–216°C; Yield-82%; ^{1}HNMR (400 MHz, $CDCl_3$) : 11.417 (s, 1H, NH, imidazole), 8.074 (d, J=7.2 Hz, 2H, aromatic), 7.914–7.297 (m, 13H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): 150.08, 138.45, 135.97, 131..71, 130.21, 129.88, 128.80, 128.18, 127.87, 127.21, 126.07; LCMS (m/z); 297.87(M^++H); Molecular formulae: $C_{21}H_{16}N_2$; Elemental analysis: Calculated: C-85.11, H- 5.43, N- 9.44; Obtained: C- 85.05, H -5.41, N-9.53.

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

Palered; M.p: 221–223°C. Yield-90%; ^{1}HNMR (400 MHz, $CDCl_3$) δppm: 11.418 (s, 1H, NH-imidazole), 9.254 (s, 1H, OH), 7.890 (d, J=7.0Hz, 2H), 7.579–7.294 (m, 10H, Ar-H), 7.047 (d, J=8.0 Hz, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δppm: 158.03, 147.15, 128.55, 125.75, 123.87, 120.89, 114.77, 115.81, 102.67, 98.46; LCMS (m/z); 313.17(M++H); Molecular formulae : C_{21} H_{16} N_2O ; Elemental analysis : Calculated : C-80.74 ,H- 5.15 , N-8.97 ; Obtained : C- 80.67 ,H – 5.14 , N- 9.08.

2.2.3. 2-(2, 4, 6-Trimethoxyphenyl)-4, 5-diphenyl-1Himidazole (4c):

Palered; M.p:238-240°C ; Yield-61%; ^{1}HNMR (400MHz,$CDCl_3$) δppm: 11.518 (s, 1H, NH imidazole), 7.894-7.412 (m, 10H, Ar-H), 7.254-7.054(m, 2H, Ar-H), 3.724(s,3H, OCH_3),3.625(s,6H,2.OCH_3);^{13}CNMR(100MHz,$CDCl_3$)δppm:154.55,152.26,147.19, 142. 32,135.71,132.66,131.95,128.77,128.51,128.02,127.54,125.96,118.67,115.58,114.80, 112. 12, 55.57, 54.71. LCMS (m/z); 387.871 (M+H); Molecular formulae: C_{24} H_{22} N_2 O_3; Elemental analysis: Calculated: C- 74.59, H- 5.73, N-7.25; Obtained: C- 74.52, H- 5.72, N- 7.35.

2.2.4. 2-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazole (4d):

Palered; Yield-88%;M.p 228-230°C; ^{1}HNMR (400MHz, $CDCl_3$)δ ppm: 11.719 (s, 1H, NH-imidazole), 8.217 (d, J=8.0 Hz, 2H, Ar-H), 7. 887-7.574 (m, 12H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$)δppm :151.28, 139.96, 134.08, 132.74,

130.05, 129.55, 128.86, 128.51, 128.22, 128.10, 128.01, 127.88, 127.43, 126.17, 125.25; LCMS (m/z); 322.22 (M+2); Molecular formulae: C_{21} $H_{15}Cl$ N_2; Elemental analysis: Calculated: C- 76.25 , H-4.56 , N- 8.46 ; Obtained: C- 76.17, H-4.55, N- 8.54.

2.2.5. 2-(4-Bromophenyl)-4,5-diphenyl-1H-imidazole (4e):

Palered; Yield-88%; MP-232-234ºC;^{1}HNMR ($CDCl_3$, 400MHz) ppm: 11.365(s, 1H, NH), 8.154(d, J= 9.4 Hz, 2H), 7.887 (d, J= 8.0 Hz, 2H), 7.754-7.274 (m, 10H, Ar-H); ^{13}C NMR (100MHz,$CDCl_3$)δ *ppm*:149.17, 139.68, 136.58, 132.78, 130.08, 129.44, 129.03, 128.91, 128.55, 128.04, 127.84, 127.32, 127.04, 126.51, 122.63. LCMS (m/z); 376.87 (M+2); Molecular formulae: C_{21} $H_{15}Br$ N_2; Elemental analysis: Calculated: C- 67.21, H- 4.02, N-7.46; Obtained: C-67.14, H -4.01, N- 7.53.

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

Palered; Yield-86%; M.p:234-236°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ *ppm*: 11.884 (s, 1H, NH-imidazoles) 8.114 – 7.290 (m, 14H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$)δ ppm: 151.07, 138.79, 136.15, 131.36, 129.88, 129.08, 128.93, 128.55, 128.11, 127.66, 119.24,115.77;LCMS(m/z);322.54; Molecular formulae : C_{22} H15 N_3; Elemental analysis : Calculated : C- 82.22 ,H-4.70 , N-13.08 ; Obtained : C- 82.14 ,H – 4.68 , N- 13.17.

2.2.7.. 2-(4-Nitrophenyl)-4.5-diphenyl-1H-imidazole (4g):

Palered; Yield-84%; MP -232-234 ºC; ^{1}H NMR (400MHz, $CDCl_3$)δppm : 11.754 (s,NH-imidazole,1H),8.218-7.347 (m, 14H, Ar-H). 13C NMR (100MHz, CDCl3)δppm: 119.54, 122.40, 124.05, 125.44, 126.18, 126.49, 127.50, 128.44, 129.27, 130.76, 136.81, 141.10, 152.70. LCMS (m/z);342.37(M+H); Molecular formulae: C_{21} H_{15} N_2O_3 ; Elemental analysis : Calculated : C- 73.89 ,H- 4.43 , N- 12.31 ; Obtained : C- 73.81 ,H -4.41 , N- 12.39.

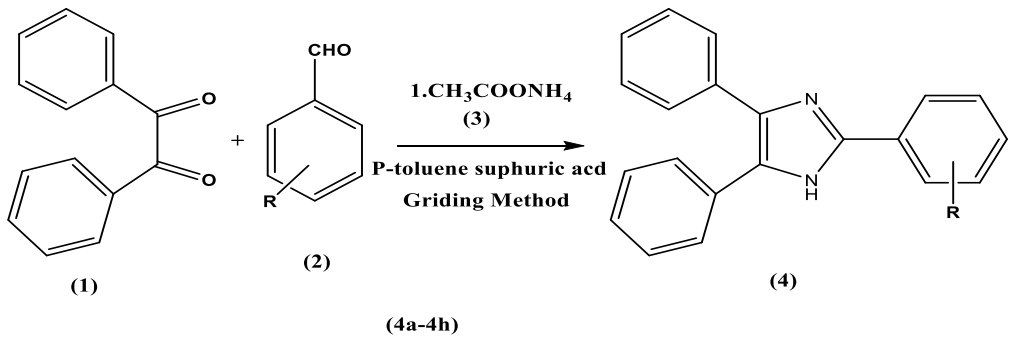
3. BIOLOGICAL ACTIVITY:

ANTI-BACTERIAL ACTIVITY:

The anti-bacterial activities of titled derivatives are evaluated against four pathogenic bacteria strains .The results of this bacterial activity were identified for tested samples. The gram negative bacteria were screened against E.coli, P. aeruginosa. The gram positive bacteria screened were examined against S-aureas and Bacillus. The target compounds were used at the different concentration and average value calculated and using DMSO as a solvent the amoxylin 10 µg/ml discs were used as a standard. The rest of the compounds were found to be moderate active against the tested microorganism.

4.RESULTS AND DISCUSSION:

4.1.Chemistry:



(1) (2) (4)

(4a-4h)

R = H, 4-OH,2,5-(OMe)2, 3,4,5 $(OMe)_2$, 4-Cl, 4-Br , 4-NO_2, 4-CHO

(Scheme-1)

In this synthesis, initially we start the preparation of titled analogous (4a-4g) from the reaction between three component were used to follow the grinding process. This type technic applied the synthesis of desired compounds is very useful and other advantages achieved. An efficient synthesis of 2,4,5-trisubstituted imidazoles is prepared by three component cyclocondensation of 1,2-dicarbonyl compounds, substituted aryl aldehydes and ammonium acetate in presence of PTSA as catalyst followed by grinding method as shown in scheme-1

Table-I Antimicrobial activity screening activity synthesized scaffold.

Entry	Bacteria			
	S.aureus	E.coli	S. typhi	B.substill
4a	06	08	09	10
4b	16	17	16	17
4c	17	18	17	19
4d	21	20	21	21
4e	22	21	20	22
4f	09	10	11	11
4g	10	08	09	09
Amoxicillin	25	25	27	27
DMSO	-	-	-	-

4.2.BIOLOGICAL ACTIVITY:

All the synthesized derivatives were evaluated by anti-bacterial activity as well as antifungal Activity. The electron attracting group of compounds and electron donating group compounds showed different activity against the all bacterial and fungal strains. Therefore, electron withdrawing group of derivatives exhibited poor biological activity compared with electron releasing groups. All halogen compounds exhibited good to excellent activity even though, these are electron attracting groups but also having lephoplic nature. The compound which possess electron donating group showed moderate activity as shown in Table-I. The compound were containing halogen family of aldehydes, which exhibited excellent activity

5. CONCLUSION:

Multicomponent reactions encouraged an outstanding status in organic synthesis 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 imidazoles is acquired by three component cyclocondensation of benzil, substituted aromatic aldehydes and ammonium acetate as ammonia source in grinding method using Bronsted acidic catalyst PTSA as catalyst. The key advantages of this process are cost effectiveness of catalyst, easy work-up and purification of products by non-chromatographic methods, excellent yields and very short time reactions.

6. AKOWNLDEMENT:

We would like to acknowledge PRISM PG &DG College, Visakhapatnam for providing us laboratory facility to carry out project work.

7. REFERENCES:

[1]. Saikat Das Sharma, Parasa Hazarika, Dilip Konwar An efficient and one-pot synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles catalyzed by $InCl_3 3H_2O$, Tetrahedron Letters 49, 2216-2220, 2008.

[2] Prisinano, T.; Law, H.; Dukat, M.; Slassi, A.; MaClean, N.; Demchyshyn, L.; Glennon, R. A. Bioorg. Med. Chem., 9, 613, 2001.

[3] Bhor, S.; Anilkumar, G.; Tse, M. K.; Klawonn, M.; Döbler, C.; Bitterlich, B.; Grotevendt, A.; Beller, M. Org. Lett., 7, 3393, 2005.

[4] Lambardino, J. G.; Wiseman, E. H. J. Med. Chem., 17, 1182, 1974.

[5] Takle, A. K.; Brown, M. J. B.; Davies, S.; Dean, D. K.; Francis, G.; Gaiba, A.; Hird, A. W.; King, F. D.; Lovell, P. J.; Naylor, A.; Reith, A. D.; Steadman, J. G.; Wilson, D. M. Bioorg. Med. Chem. Lett., 16, 378, 2006.

[6] Hojat Veisi, Ardashir Khazaei, Leila Heshmati, and Saba Hemmati, Convenient One-Pot Synthesis of 2,4,5-Triaryl-1Himidazoles Bull. Korean Chem. Soc., 33, 4, 1231, 2012.

[7] Lee, J. C.; Laydon, J. T.; McDonnell, P. C.; Gallagher, T. F.; Kumar, S.; Green, D.; McNulty, D.; Blumenthal, M. J.; Keys, J. R.; Vatter, S. W. L.; Strickler, J. E.; McLaughlin, M. M.; Siemens, I.

R.; Fisher, S. M.; Livi, G. P.; White, J. R.; Adams, J. L.; Young, P. R. Nature, 372, 739, 1994.

[8] Takle, A. K.; Brown, M. J. B.; Davies, S.; Dean, D. K.; Francis, G.; Gaiba, A.; Hird, A. W.; King, F. D.; Lovell, P. J.; Naylor, A.; Reith, A. D.; Steadman, J. G.; Wilson, D. M. Bioorg. Med. Chem. Lett., 16, 378, 2006.
[9] Khanna, I. K.; Weier, R. M.; Yu, Y.; Xu, X. D.; Koszyk, F. J.; Collins, P. W.; Koboldt, C. M.; Veenhuizen, A. W.; Perkins, W. E.; Casler, J. J.; Masferrer, J. L.;Zhang, Y. Y.; Gregory, S. A.; Seibert,K.; Isakson, P. C. J. Med. Chem., 40, 1634, 1997.

[10] Lange, J. H. M.; Van Stuivenberg, H. H.; Coolen, H. K. A. C.; Adolfs, T. J. P.; McCreary, A. C.; Keizer, H. G.; Wals, H. C.; Veerman, W.; Borst, A. J. M.; de Loof, W.; Verveer, P.C.; Kruse, C. G. J. Med. Chem., 48, 1823, 2005.

[11] Gallagher, T. F.; Fier-Thompson, S. M.; Garigipati, R. S.; Sorenson, M. E.; Smietana, J. M.; Lee, D.; Bender, P. E.; Lee, J.C.; Laydon, J. T.; Griswold, D. E.; Chabot-Fletcher, M. C.; Breton,

J. J.; Adams, J. L. Bioorg. Med. Chem. Lett., 5, 1171, 1995.[12] de Laszlo, S. E.; Hacker, C.; Li, B.; Kim, D.; MacCoss, M.; Mantlo, N.; Pivnichny, J. V.; Colwell, L.; Koch, G. E.; Cascieri, M. A.; Hagmann, W. K. Bioorg. Med. Chem. Lett., 9, 641, 1999.

[13] Eyers, P. A.; Craxton, M.; Morrice, N.; Cohen, P.; Goedert, M. Chem. Biol., 5, 321, 1998.

[14] Newman, M. J.; Rodarte, J. C.; Benbatoul, K. D.; Romano, S. J.; Zhang, C.; Krane, S.; Moran, E. J.; Uyeda, R. T.; Dixon, R.; Guns, E. S.; Mayer, L. D. Cancer Res. 60, 2964, 2000.

[15] Antolini, M.; Bozzoli, A.; Ghiron, C.; Kennedy, G.; Rossi, T.; Ursini, A. Bioorg. Med. Chem. Lett. 9, 1023, 1999.

[16] Wang, L.; Woods, K. W.; Li, Q.; Barr, K. J.; McCroskey, R. W.; Hannick, S. M.; Gherke, L.; Credo, R. B.; Hui, Y.-H.; Marsh, K.; Warner, R.; Lee, J. Y.; Zielinsky- Mozng, N.; Frost, D.; Rosenberg, S. H.; Sham, H. L. J. Med. Chem., 45, 1697, 2002

.[17] Maier, T.; Schmierer, R.; Bauer, K.; Bieringer, H.; Buerstell, H.; Sachse, B. U.S. Patent 4820335, 1989; Chem. Abstr., 111, 19494w, 1989.

[18] Chowdhury, S.; Mohan, R. S.; Scott, J. L. Reactivity of ionic liquids, Tetrahedron, 63, 2363, 2007.

[19] Adel A. Marzouk, Vagif M. Abbasov and Avtandil H. Talybov, Short Time One-Spot Synthesis of 2, 4, 5-TrisubstitutedImidazoles Using Morpholinium Hydrogen Sulphate as Green and Reusable Catalysts, Chemistry Journal, 02, 05, 179-184, 2012.

[20]. Freedman J., Loscalzo J. New Therapeutic Agent in Thrombosis and Thrombolysis, Third Edition, Taylor and Francis, 2009.

[21].Shaterian H. R., Mohammad R., An environmental friendly approach for the synthesis of highly substituted imidazoles using Brønsted acidic ionic liquid, N-methyl-2-pyrrolidonium hydrogen sulfate, as reusable catalyst, Journal of Molecular Liquids, 160,

40-49, 2011.

[22] Ali M., Hossein K., Reza S., Behrooz M., Hamed R., Hassanali M., Zeinalabedin S., Saman D., A highly efficient and reusable heterogeneous catalyst for the one-pot synthesis of tetra substituted imidazoles, Applied Catalysis A: General, 429-430, 73-78, 2012.

[23]. Singh, P.; Kumar, R.; Tiwari, S.; Khanna, R.S.; Tewari, A.K.; Khanna, H.D. Docking, synthesis and evaluationof antioxidant activity of 2,4,5-triaryl imidazole. Clin. Med. Biochem. Open Access 2015, 1, 105.

.