IJMPR 2024, 8(5), 72-76

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Research Article

SJIF Impact Factor: 6.669

AN EFFICIENT SOLVENT FREE ONE-POT SYNTHESIS OF 2-PHENYL-1H-BENZIMIDAZOLE DERIVATIVES BY ORGAN CATALYST AND EXPLORING ANTIMICROBIAL ACTIVITY

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Article Received on: 15/03/2024
Article Revised on: 05/04/2024
Article Accepted on: 25/04/2024

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ABSTRACT

As a part of our research programed, in present study of the developed method for the synthesis of some novel analogous of 2-phenyl-1H-benzimidazole employing Bronsted acid catalyst that contain the basic skeleton in numerous bioactive derivatives. The newly prepared compounds were synthesized from the condensation of reaction between O-Phenylenediamine and various substituted aryl aldehyde in the presence of trifluoro acetic acid in aqueous medium. The yield of all newly derivatives synthesized compounds was found to be in the range of 85-95%. The synthesized compounds were evaluated by using ^{1}HNMR, ^{13}CNMR and MASS spectral data together with elemental analysis. In addition to examined the biological activity.

KEYWORDS: O-phenylimino, substitutedaromaticaldehydes, Trifluoroaceticacid, 2-phenyl-1H-benzimidazole derivatives, Antimicrobial activity.

1. INTRODUCTION

The Benzimidazole possesses benzene ring fused to a five member heterocyclic aromatic imidazole ring. They have been also named as o-Phenylenediamine derivatives.[1] The Benzimidazole is also known as benziminazoles or benzoglyoxalines. Benzimidazole nucleus that covered by large area of wide interest because of their diverse biological and biological applications .Moreover, Benzimidazole derivatives are structural isosters of naturally occurring nucleotides, which also allows them to interact easily with the biopolymers of the living system.

Benzimidazoles are considered an important class of bioactive fused heterocyclic compounds that exhibit wide range of pharmocolical properties. Especially, this nucleus is a containing vitamin-B12. This ring system is present in various anticonvulsant[2], anthelmintic[3], antihepatic[4], anti-HIV[5], anti-inflammatory[6], antiprotozoal[7], and antineoplastic[8], antiulcer[9], activities. The derivatives of Benzimidazole with different pharmacological effects, including antifungal[10], cardio tonic[11], and neuroleptic[12] and analogous of benzimidazoles were e found to appreciation in diverse therapeutic areas of antimicrobial activity.[13,15] In the previous reports, we analyzed the synthesis of a number of benzimidazoles analogous with biological properties.[16,18]

The yields of these products were significantly developed and the rate of reaction and time factor was reduced when the named derivatives were produced under these conditions using a commonly accessible separable desired catalyst. Thus, we would want to present a rapid and simple method that uses trifluoro acetic acid as a catalyst to create hexahydroquinazolinone derivatives without the requirement for a solvent free

2. MATERIALS AND METHODS:

All the reagents, solvents and analytical grade and were procured from Merck chemicals and are used as such solvents without further purification. The reaction was checked by thin-layer chromatography (TLC, eluent Hexane: ethyl acetate 3:7). The newly synthesized compounds were evaluated by ^{1}HNMR, ^{13}CNMR and Mass spectroscopy. ^{1}H NMR and ^{13}CNMR spectra were recorded on a Broker Avance 400 MHz-100MHz instrument in$CDCl_3$ using Tetramethylsilane (TMS) as an internal standard. The mass titled compounds were weighed by .Mass Spectrometry (LCMS) Agilent mass spectrometer. The melting points of titled derivatives were determined by a Buchi-510 apparatus and were uncorrected.

2.1. Experimental Procedure for the Synthesis of Benzimidazoles derivatives

Take dry and clean four neck 50 mL RBF and mixture of substituted aromatic aldehyde (1.125mmol) was added to

a stirred solution of 1, 2-phenylenediamine (1.125mmol) and trifluoro aceticacd (2.5mmol) in water (25 ml) for five minutes at reflux and Stirring was continued for two hours. The progress of the reaction was checked with help of TLC. After completion of the reaction (TLC, eluent Hexane: ethylacetae 7:3), the solvent was removed under reduced pressure and extracted with ethyl acetate three washings and the organic layer was washed with Braine water (25 ml). Organic layers were separated and the organic layer was dried over sodium sulfate. The solvent was removed under reduced pressure and the crude product was subjected to column chromatography using petroleum ether: EtOAc (6:4), which gave desired product as a solid in 85-95% yield.

2.2. Characterization of Benzimidazoles derivatives

2.2.1.2-phenyl-1H-benzimidazole (3a)

whiteSolid; Yield-87%, m.p-208-210^{o}C; Rf-0.450 (n-hexane:EtOAc-7:3); ^{1}HNMR (400MHz,$CDCl_3$) δppm: 10.245 (s,1H,NH),8.110-7.683 (m, 2H, Ar-H), 7.586-7.297 (m, 7H, Ar-H); ^{13}CNMR (100MHz, $CDCl_3$) δppm: 154.25, 141.54, 138.58, 130.53, 129.92, 128.96, 127.09, 123.58, 121.49, 118.77, 111.56. LCMS (m/z*):* 195.12 (M+H), Molecular formula: $C_{13}H_{10}N_2$.

2.2.2.4-(1H-benzimidazol-2-yl) phenol (3b)

Solid;Yield-93%,m.p-228-230^{0}C;Rf-0.445(n-hexane:EtOAc-7:3);1HNMR(400MHz,$CDCl_3$) δppm: 10.241 (s, 1H, NH), 8.784 (s, 1H, -OH); 7.845-7.298 (m, 8H, Ar-H); ^{13}CNMR (100MHz, $CDCl_3$) δppm: 154.57, 150.85, 141.56, 129.85, 123.52, 119.16, 116.54, 112.77; LCMS(m/z): 211.34 (M+H). Molecular formula: $C_{13}H_{10}N_2O$.

2.2.3.2-(4-methoxyphenyl)-1H-benzimidazole (3C)

Palebrowncompound;Yield-95%,m.p-236-238^{0}C:Rf-0.450(n-hexane:EtOAc-6:4);1HNMR(400 MHz, $CDCl_3$): δ3.672 (s, 3H, OCH_3), 6.106 (s, 1H, NH), 6.979 (d, J=8.0Hz, 2H,aromatic), 7.112 (d, J=7.2 Hz, 2H, Ar-H, 7.256 (d, J=6.8Hz, 2H, Ar-H), 7.64 (d, J=9.2Hz, 2H, Ar-H), ^{13}CNMR (100MHz, $CDCl_3$) δppm: 161.55, 151.88, 130.74, 128.48, 123.86, 122.44, 113.01, 55.75. LCMS (m/z): 225.45 (M^++H). Molecular formula: $C_{14}H_{12}N_2O$.

2.2.4.2-(3, 5-Dimethoxyphenylhenyl)-1H-benzimidazole (3d)

Paleredsolid; Yeild: 95%; m.p-241-243^{0}C; Rf-0.450 (n-hexane: EtOAc-5: 5); 1HNMR (400 MHz, $CDCl_3$) δppm: 11.514 (s, 1H, NH), 7.770-7.122 (m, 7H, Ar-H), 3.764 (s, 3H, OCH_3), 3.568 (s, 3H, OCH_3): ^{13}CNMR (100MHz, $CDCl_3$) δppm: 152.86, 147.37, 138.81, 124.04, 122.87, 121.58, 116.71, 113.88, 110.46, 56.82. LCMS (m/z): 254.51 (M^+-H); Molecularformule: $C_{15}H_{14}N_2O_2$.

2.2.5.2-(4-Chlorophenyl)-1H-benzimidazole (3e)

Whitecompound: Yield-91%, m.p-248-250^{o}c, Rf-0.450 (n-hexane: EtOAc-6:4); 1HNMR (400 MHz, $CDCl_3$) δppm: 11.516 (s, 1H, NH), 7.878 (d, J=5.6Hz, 2H), 7.554-7.234 (m, 2H, Ar-H), 7.150-7.054 (m, 2H, Ar-H), ^{13}CNMR (100MHz, $CDCl_3$) δppm: 152.59, 142.88, 135.22, 130.89, 128.45, 127.85, 123.94, 122.78, 118.55, 112.26. LCMS (m/z): 194.14. Molecularformule: $C_{13}H_9ClN_2$.

2.2.6. 2-(4-Hydroxy-2-bromophenyl)-1H-benzimidazole (3f)

Paleredsolid: yeild: 95%; 250-252^{0}C; Rf-0.424 (n-hexane: EtOAc-7:3); 1HNMR (400MHz, $CDCl_3$): δppm= 10.512 (s, 1H, NH), 7.841-7.408 (m, 7H, Ar-H), 5.448 (s, 1H, NH), ^{13}CNMR (100MHz, $CDCl_3$) δppm:-154.42, 148.88, 142.08, 130.89, 129.66, 127.94, 123.83, 119.06, 117.55, 115.77: (LCMS) m/z: 288.21 (M^++H): Molecularformule: $C_{13}H_9N_2BrO$.

2.2.7. 4-(1H-benzo[d]imidazol-2-yl) benzonitrile (3g)

White solid, Yield-90%, m.p-255-257^{0}C; Rf-0.450 (n-hexane: EtOAc-6:4); ^{1}HNMR (400 MHz, $CDCl_3$): δppm: 11.214 (s, 1H, NH), 7.758-7.361 (m, 8H, Ar-H); ^{13}CNMR (100MHz, $CDCl_3$) δppm: 152.96, 143.51, 136.65, 129.77, 127.66, 122.82, 118.59, 115.7, 112.7; LCMS (m/z): 217.38 (M^+); Molecularformule: $C_{14}H_9N$.

2.2.8.2-(4-nitrophenyl)-1H-benzimidazole (3h)

whitesolid, Yield-87%, m.p-247-249^{0}C; Rf-0.450 (n-hexane: EtOAc-7:3); 1HNMR (400MHz, $CDCl_3$) δppm: 11.492 (s, 1H, NH), 7.852 (s, 1H), 7.75 (d, J= 7.6Hz, 1H, Ar-H), 7.66 (d, J= 9.6Hz, 1H, Ar-H), 7.659-7.409 (m, 1H, Ar-H), 7.222 (t, J = 8.0Hz, 2H, Ar-H). ^{13}CNMR (100MHz, $CDCl_3$) δppm: 153.65, 147.55, 136.46, 130.09, 128.28, 126.02, 122.43, 120.51, 119.85, 118.57, 116.56, 110.8. LCMS (m/z): 239.25. Molecular formulae: $C_{13}H_8N_3O_2$.

3. BIOLOGICAL ACTIVITY

3.1. Antimicrobial Activity

The antimicrobial activities of all desired compounds were evaluated by disc diffusion method using Mueller-Hinton agar medium and also study the preliminary test of antibacterial activity against pathogens such as S.aureus, E.coli, Typhi and B.substills.. The agar medium was purchased from HI media laboratories Ltd., Mumbai, India. Nutrient broth, subculture, base layer medium, agar medium and peptone water were prepared as per this standard procedure. Each of the target compounds was dissolved in 10 mL of dimethyl sulfoxide Volume of 0.05ml and 0.1ml of each compound was used for testing**"Streptomycine**" as a standard drug antimicrobial activity.

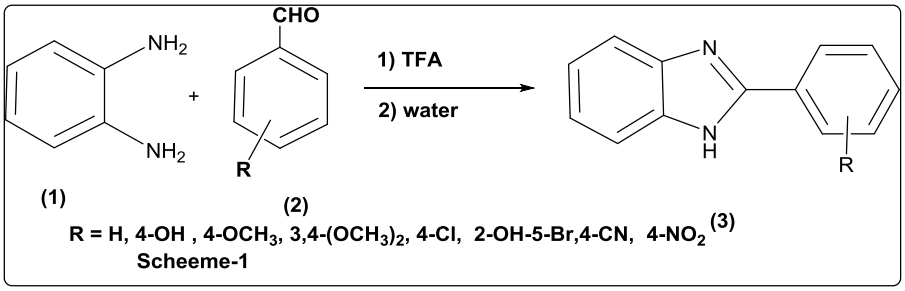
The PDA medium was employed to study the preliminary antifungal activity against Aspergillus Niger and Candida albicans by used to the cup plate method. The PDA medium was procured from HI media laboratories Ltd. Mumbai, India. Agar medium, peptone water, subculture, Nutrient broth and base layer medium were obtained as per the standard procedure. Each target compound was dissolved in 10mL of dimethyl sulfoxide volume of and 1mg/ml of each compound were used for testing Fluconazole "was used as standard drug of antifungal activity and dimethyl sulfoxide as a control.

The observed zone of inhibition was measured in mm and results are present in table III.

RESULTS AND DISCUSSION

Reactions were carried out by taking a 1:1 mol ratio mixture of O-Phenylenediamine with substituted aromatic aldehyde in the presence of trifluoro acetic acid in aqueous medium to give derivatives of 2-phenyl-1H-benzimidazole **(Scheme-1).**

The synthetic pathway for the synthesis of the benzimidazoles derivatives listed in the Table is shown in the Scheme. Nucleophilic additions of O-pheyldiamine with substituted aromatic aldehyde were used for the next step without purification. The reaction of substituted aromatic aldehyde with O-pheyldiamine scaffold the desired analogue us Benz imidazole A structural evaluation of the new synthesized derivatives Benzimidazole can be synthesized in this study was performed using various spectroscopic techniques. Various researchers reported a synthesis of Benzimidazole derivatives, but in our present study we synthesized the Benz imidazole derivatives by using trifluoro acetic acid catalysts, which were in expensive and decreased there action time, with very moderate to good yields. This method could be easily practiced in laboratories within the stipulated time.



Scheme-I of 2-phenyl-1H-benzimidazole Derivatives.

The reaction is carried out, the required amount of catalyst for this reaction, **4-hydroxy-2-bromo benzaldehyde** was used as a model compound for optimization and various amounts of catalyst were examined under the reflux conditions. It was found that3.0 mol% of catalyst was enough for a fairly good yield **(Table 1).** On the other hand, an amount of catalyst over than 3.0 mol% did not develop the yield of product.

Table 1: Reaction of O-Phenylene diamine with 2-(3, 5-Dimethoxy phenylhenyl)-1H-benzimidazole in aqueous medium using different amounts of catalyst at reflux.

Entry	Mol% Catalyst	Time (h)	Yield (%)
1	2.0 mol	2.5	75
2	3.0 mol	3.0	95
3	4.0 mol	3.5	87
4	5.0 mol	4.0	87

We observed that the effect of solvent for this example of the reaction, we have also performed the reaction in different organic solvents at room temperature with 3 mol% of camphorsulfonic acid As Table II shows, the most important suitable solvent for this procedure is aqueous medium Consequently, the reaction was carried out in water with 3.0 mol% of camphorsulfonic acid for the preparation of Benzimidazole (3a-h). The results are summarized in Table II and Table III. Reaction of o-Phenylenediamine with 4-hydroxy-2-bromo benzaldehyde using different solvents, Prompted by 3.0 mol% camphorsulfonic acid in aqueous medium under reflux condition.

Table II: Reaction of O-Phenylene diamine with 2-(3, 5-Dimethoxyphenylhenyl)-1H-benzimidazole using various solvent under reflux.

Entry	Solvent	Time (h)	Yield (%)
1	H_2O	3.0	95
2	Ethanol	3.0	89
3	Methanol	3.5	70
4	DMF	4.0	69
5	DMSO	4.5	67
6	Acetonitrile	4.5	54

The ^{1}H and ^{13}C NMR spectra as well as the elemental analyses data of all newly synthesized compounds are containing with the expected structures. The ^{1}H NMR and ^{13}CNMR spectra of benzimidazoles **(3a-h)** consists

of a multiplet and a broad singlet at downfield shift resulting from the aromatic protons and the NH group respectively.

The investigation of antibacterial evaluation data showed that the compounds **"3e"** highest antibacterial activities against *E. coli*, as gram negative bacteria (Table III). Also compounds **"3c, 3d and 3f"** exhibit good inhibition against *S. aureus* as compared to streptomycin zone of inhibition. While the investigation of antifungal evaluation data **"3f"** showed good fungal activity as compared to Fluconozole.

Table III: Antimicrobial activity screening activity synthesized by camphorsulfonic acid scaffold.

Compound Code	*Zone of inhibition in (mm)					
	Bacteria				Fungi	
	S.aureus	E.coli	S. typhi	B.substills	A. niger	C. albicans
3a	07	08	09	07	05	04
3b	15	21	11	25	07	08
3c	18	24	10	26	06	08
3d	17	24	15	25	17	21
3e	22	18	12	19	11	09
3f	20	19	18	19	20	19
3g	15	18	12	17	16	17
3h	09	10	09	11	15	13
Streptomycin	30	30	30	30	---	----
Fluconazole	---	---	---	---	-25	25
DMSO	10	10	10	10	10	10

CONCLUSION

In conclusion, we have enhanced a simple and high efficient procedure for the synthesis of 2-phenyl-1H-benzimidazole derivatives with advantages of operational simplicity, good to high yields and use of non-toxic and commercial available catalyst viz; trifluoro acetic acid . Antimicrobial activity of titled compounds can be examined by suitable standard drugs and also acquired moderate to good active potential and yield of newly synthesized compound.

REFERENCES

1. John B. Wright, January 29, (1951) The chemistry of the Benzimidazoles, Research Laboratories, The Upjohn Company, Kalamazoo, Michigan, 1951.
2. Kalappa M. Hosmani, Rangappa S. Keri, derivative of benzimidazole pharmacophore: Synthesis, anticonvulsant, antidiabetic and DNA cleavage studies". Euopean Journal of Medicinal Chemistry, 2010; 45: 1753-1759.
3. M Himaja Rajiv, MV Ramana, Synthesis of 6-Nitrobenimidazol-1-acetyl amino acids and peptides as potent anthelmintic agents". Indian Journal of Hetero cyclic Chemistry, 2002; 2: 121-2.
4. Yu. Luo, Jia- Ping Yao, "Design and synthesis of novel benzimidazole derivatives as inhibitors of Hepatitis B Virus". Bioorganic & medicinal Chemistry letters, 2010; 18: 5048-5055. 124.
5. John M. Gardiner, Synthesis and HIV inhibition of novel benzimidazole derivatives", Bioorganic and medicinal chemistry letters, 1995; 5: 1251-1254. Gardiner.
6. Kallappa M. Hosamani, In-vivo analgesic and anti-inflammatory activities of newly synthesized benzimidazole derivatives, European Journal of Medicinal Chemistry, 2010; 45: 2048–2054.
7. Lilián Yépez-Mulia, Rafael Castillo, Synthesis and biological activity of 2-(trifluoromethyl)-1H-benzimidazole derivatives against some protozoa and Trichinella spiralis, European Journal of Medicinal Chemistry, 2010; 45: 3135-3141.
8. V. Murugan, K. Ramaprasad, Synthesis of triazoles thiadiazole and oxadiazole bearing 2-thiomethyl benzimidazole and their biological evaluation, Indian Journal of Hetero cyclic Chemistry, 2001; 11: 169-170.
9. Richard L Lombardy, Farial A Tanious, Synthesis and DNA interaction of benzimidazole dication which have activity against opportunistic infections, Journal of Medicinal Chemistry, 1996; 39: 1452-1462.
10. KH Berg; M Buchel; A Plempel; Zywietz; Mykosen, 1986; 29: 221-229.
11. G Piazzesi; L Morano; JC Ruegg. Arzneim Forsch. *Drug Res.*, 1987; 37: 1141-1143.
12. AJ Janssen; FTN Allewijn; F Arzneim. *Drug Res.*, 1968; 18: 279-282.
13. LN Divaeva; TA Kuzmenko; AS Morkovnik; VN Komissarov. *Chem. Heterocyclic Compds.*, 2006; 42: 463-468.
14. A Davoodnia; M Roshani; E Saleh Nadim; M Bakavoli; N Tavakoli Hoseini. *Chin. Chem. Lett.*, 2007; 18: 1327-330.
15. C Kus; G Aylan-Kicigil; M Iscan. *Arch. Phar, Res.*, 2004; 27: 156-163.
16. Gogoi P and Konwar D. An efficient and one-pot synthesis of and benzimidazoles viaanaerobic oxidation of carbon-nitrogen bonds in water.*trahedron Lett.*, 2006; 47: 79-82.
17. Cadamic Press, Harcourt Brace and Company Publishrs, 1997; 71-94.

18. Han X, Ma H and Wang Y. A simple and efficient synthesis of 2-aryl-substituted benzimidazoles. *Russ. J. Org. Chem*., 2008; 44: 863-865.