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

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ABSTRACT

As a part of our research, in present report an improved process for the synthesis of some novel derivatives of2-phenyl-1H-benzimidazole employing organo acid catalyst which possesses the basic skeleton in various bioactive compounds. The newly synthesized compounds was obtained from the condensation of reaction between O-Phenylenediamine and various substituted arylaldehydein the presence of camphor sulfonic acid in aqueous medium. The yield of all newly derivatives synthesized compounds was found to be in the range of 90 - 95%. The synthesized compounds were characterized by using ^{1}HNMR, ^{13}CNMR and MASS spectral data together with elemental analysis. In addition to evaluate the biological properties.

KEYWORDS

O-phenyldiamine, Substituted aromatic aldehyde, Camphor sulfonic acid, 2-phenyl-1H-benzimidazole derivatives and Antimicrobial activity.

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INTRODUCTON

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 are also known as benziminazoles or benzoglyoxalines. It nucleus that covered by large area of wide interest because of their diverse biological and biological applications. Moreover, Benzimidazole derivatives are structural is osters 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 pharmacological properties. Especially, this nucleus is a containing vitamin-B12. This ring system is present in various anticonvulsant[2], antihelmintics[3], antihepatic[4], anti-HIV[5], antiinflammatory[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 found to appreciation in diverse therapeutic areas of antimicrobial activity[13-18]. In the previous reports, we analyzed the synthesis of a number of benzimidazole analogous with biological properties[19-32].

MATERIAL AND METHODS

All the chemicals, reagents and solvents of analytical grade and were purchased from Merck chemicals and are used as such solvents without further purification. There action was checked by thin-layer chromatography (TLC, eluent Hexane: ethyl acetate 40: 60). The newly synthesized compounds were evaluated by ^{1}HNMR, ^{13}CNMR and Mass spectroscopy. ^{1}HNMR and ^{13}CNMR spectra were recorded on a Brooker avance 400MHz-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 newly synthesized compounds were determined by a Buchi-510 apparatus and were uncorrected.

Experimental Procedure for the Synthesis of Benzimidazoles derivatives

Substituted aryl aldehyde (1.2mmol) was added to a stirred solution of 1, 2-phenylenediamine (1mmol) and camphor sulfonic acid (3mmol) in water (10ml) for five minutes at reflux and Stirring was continued for three hours. The reaction was monitored with help of TLC. After completion of the reaction (TLC, eluent Hexane: ethyl acetate 6: 4), the solvent was removed under reduced pressure and extracted with ethyl acetate three washings and the organic layer was washed with brain water (10ml). 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 90-95% yield.

Characterization of Benziminazoles derivatives

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

White Solid; Yield-91%, m.p-285-286^{o}C; ^{1}HNMR (400MHz, $CDCl_3$) δppm: 10.91 (bs, 1H, NH), 8.10-7.83 (m, 2H, CH aromatic), 7.56-7.33 (m7H, CH aromatic); ^{13}CNMR (100MHz, $CDCl_3$) δppm: 153.5, 142.5, 137.8, 130.3, 129.2, 128.6, 125.9, 123.8, 121.9, 118.7, 111.6. LCMS (m*/z):*193.54 (M-H) +. Molecular formula: $C_{13}H_{10}N_2$.

2)4-(1H-benzimidazol-2-yl) phenol (3b):

Solid; Yield-93%, m.p-264-266^{o}C; 1HNMR (400MHz, $CDCl_3$) δppm: 10.29 (bs, 1H, NH), 8.96 (s, 1H, -OH); 7.45-6.98 (m, 8H, Ar-H); ^{13}CNMR (100MHz, $CDCl_3$) δppm: 156.7, 151.5, 141.6, 129.5, 122.2, 118.6, 116.4, 112.7LCMS (m/z):211.34 (M^+ + H). Molecular formula: $C_{13}H_{10}N_2O$

2-(4-methoxyphenyl)-1H-benzimidazole (3C)

Solid; Yield -95%, m.p-229-230^{o}C: 1H NMR (400MHz, $CDCl_3$): δ 3.72 (s, 3H , OCH_3), 6.06 (s, 1H,NH), 6.99 (d, 2H, aromatic), 7.09 (d, 2H, Ar-H, 7.26 (d, 2H, Ar-H), 7.64 (d, 2H,Ar-H), ^{13}CNMR (100MHz, $CDCl_3$) δppm: 160.5, 151.8, 130.1, 128.8, 123.6, 122.4, 113.1, 55.5. Mass (LCMS): (m/z): 225.45 (M^+ +H). Molecular formula: $C_{14}H_{12}N_2O$.

2-(3, 5-Dimethoxyphenylhenyl)-1H-benzimidazole (3d)

Colorless solid; Yield: 92%; m.p-249-251^{o}C; 1HNMR (400 MHz, $CDCl_3$) δppm: 11.03 (s, 1H, NH), 7.71-7.22 (m, 7H, Ar-H), 3.76 (s, 3H, OCH3), 3.68 (s, 3H, OCH3): ^{13}CNMR (100MHz, $CDCl_3$) δppm: 152.6, 147.7, 138.1, 124.4, 122.7, 121.8, 116.1, 113.8, 110.6, 56.2. LCMS (m/z): 254.51 (M^+-H); Molecular formulae: $C_{15}H_{14}N_2O_2$.

2-(4-Chlorophenyl)-1H-benzimidazole (3e)

Colorless solid, Yield-94%, m.p-289-290^{o}C, 1HNMR (400MHz, CDCl3) δppm: 11.16 (s, 1H, NH), 7.78 (d, 2H), 7.54-7.34 (m, 2H, Ar-H), 7.15 (m, 2H, Ar-H), ^{13}CNMR (100MHz, CDCl3) δppm:

152.9, 142.8, 135.2, 130.9, 128.5, 127.5, 123.4, 122.8, 118.55, 112.6. LCMS (m/z): 194.14. Molecular formula: $C_{13}H_9ClN_2$.

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

Pale red solid: yield: 92%; 255-256ºC; 1HNMR (400MHzCDCl3): δppm= 10.12 (s, 1H, NH), 5.48 (s, 1H, NH), 7.41-7.08 (m, 7H, Ar-H); ^{13}CNMR (100MHz, CDCl3) δppm:-153.2, 149.8, 141.0, 131.9, 129.6, 127.4, 123.3, 119.6, 116.5, 115.7: (LCMS) m/z:289.04 (M^++2): Molecular formulae: $C_{13}H_9N_2BrO$.

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

White solid, Yield-90%, m.p-261-263ºC; 1HNMR (400 MHz, $CDCl_3$): δppm=11.46 (s, 1H, NH), 7.78-7.31 (m, 8H, Ar-H); ^{13}CNMR (100MHz, $CDCl_3$) δppm: 152.6, 143.1, 136.5, 129.7, 127.6, 122.2, 118.9, 115.7, 112.7; LCMS (m/z): 217.38(M^+); Molecular formulae: $C_{14}H_9N_3$.

2-(4-nitrophenyl)-1H-benzimidazole (3h)

White solid, Yield-90%, m.p-307-309ºC; 1HNMR (400MHz, $CDCl_3$) δppm: 11.92 (s, 1H, NH), 7.82 (s, 1H), 7.75 (d, 1H, Ar-H), 7.66 (d, 1H, Ar-H), 7.59-7.40 (m, 1H, Ar-H), 7.22 (t, 2H, Ar-H). ^{13}CNMR (100MHz, $CDCl_3$) δppm: 153.5, 147.5, 136.6, 130.9, 128.8, 126.2, 122.3, 120.1, 119.5, 118.7, 116.6, 110.8. LCMS (m/z): 239.25. Molecular formulae: $C_{13}H_8N_3O_2$.

Biological Activity

Antimicrobial Activity

The antimicrobial activities of all target compounds were examined 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, S. typhi* and *B. subtilis*. 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 10mL of dimethyl sulfoxide Volume of 0.05ml and 0.1ml of each compound was used for testing "Streptomycin as a standard drug antimicrobial activity.

The PDA medium was employed to study the preliminary anti-fungal 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 No.3.

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 camphor sulfonic acid in aqueous medium to give derivatives of 2-phenyl-1H-benzimidazole (Figure No.1).

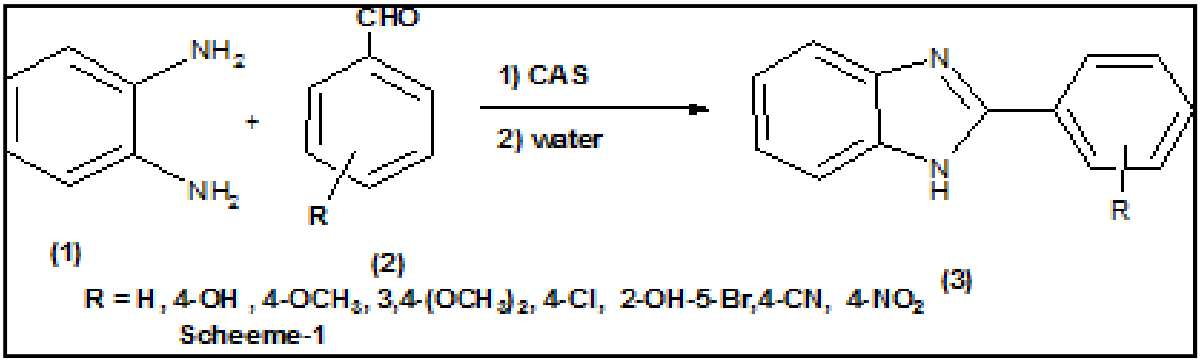
The synthetic path way for the synthesis of the benzimidazoles derivatives listed in the Table is shown in the Scheme. Nucleophilic additions of O-pheyldiamine with substituted aromatic aldehyde were used for the next step without purification. The reaction of substituted aromatic aldehyde with O-phenyl diamine scaffold the desired analogue us benzimidazole 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 benzimidazole derivatives by using camphor sulfonic 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.

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 that 3.0 mol% of catalyst was enough for a fairly good yield (Table No.1). On the other hand, an

amount of catalyst over than 3.0 mol% did not develop the yield of product.

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 3mol% of camphor sulfonic acid As Table No.2 shows, the most important suitable solvent for this procedure is aqueous medium Consequently, the reaction was carried out in water with 3.0mol% of camphorsulfonic acid for the preparation of Benzimidazole (3a-h). The results are summarized in Table No.2 and Table No.3. 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.

The ^{1}H and $^{13}CNMR$ spectra as well as the elemental analyses data of all newly synthesized compounds are containing with the expected structures. The $^{1}HNMR$ 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 evluation data showed that the compounds "3e" highest antibacterial activities against *E. coli*, as gram negative bacteria (Table No.3). 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.



Scheme No.1: 2-phenyl-1H-benzimidazole Derivatives

Table No.1: Reaction of O-Phenylenediamine with 4-hydroxy-2-bromo benzaldehyde 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	92
3	4.0 mol	3.5	87
4	5.0 mol	4.0	87

Table No.2: Reaction of O-Phenylenediamine with 4-hydroxy-2-bromo benzaldehyde using different solvent under reflux

Entry	Solvent	Time (h)	Yield (%)
1	H_2O	3.0	92
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

Table No.3: Antimicrobial activity screening activity synthesized by camphor sulfonic acid scaffold

S.No	Compound Code	*Zone of inhibition in (mm)					
		Bacteria				Fungi	
		S. aureus	*E. coli*	*S. typhi*	*B. substills*	*A. niger*	*C. albicans*
1	3a	12	10	09	07	10	09
2	3b	15	21	11	25	07	08
3	3c	18	24	10	26	06	08
4	3d	19	25	13	25	17	21
5	3e	22	18	12	19	11	09
6	3f	21	18	13	12	21	20
7	3g	15	18	12	17	16	17
8	3h	12	14	10	15	14	12
9	Stryptomycin	30	30	30	30	---	---
10	Flucnozole	---	---	---	---	-25	25
11	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; camphor sulfonic 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.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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