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Synthesis And Antimicrobial Activity Of 1-(5 Isopropoxy -2-Methyl-4-Nitrophenyl)-Substituted Benzimidazole Derivatives Via Buchwald-Hartwig Coupling

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Abstract: *The palladium-catalyzed cross-coupling of aryl halides (**2**) and N–H containing substrates (**3**) underwent Buchwald –Hartwig amination has emerged as a highly effective C–N bond-forming compounds are 1-(5-isopropoxy-2-methyl-4-nitrophenyl)-substituted benzimidazole derivatives (**4a-j**).This protocol is employed on both bench-top and industrial scales for the construction of (hetero) aryl amine. Structural elucidations of all the compounds have been accomplished by elemental analysis, [1]HNMR,[13]CNMR and Mass spectral data. They have been screened for their antibacterial activity against, three gram positive and gram negative bacterial strains.*

Keywords: *Benzimidazole, palladium-catalyzed cross-coupling-Buchwald-Hartwig amination, antibacterial activity*

I. Introduction:

Benzimidazole ring system known to be possess numerous antimicrobial[1-2], anti-inflammatory[3], anthelmintic[4],antiviral[5-7].Therefore it was enabled that the compounds containing benzimidazole nucleus would result in interesting of biological activities. Palladium catalyzed coupling reactions are extremely powerful tools to construct new C-C and C-N bonds. The mild reaction conditions of these reactions offer considerable advantages over classical methods that require either activated molecules or harsh reaction conditions. Recently, significant developments in Suzuki coupling reaction[8] and amination of aryl halide or triflate have been reported by Buchwald[9] and Hartwig[10-12].In recent years the scope of metal–mediated cross–coupling has expanded immensely, with carbon–nitrogen cross–coupling emerging to the forefront as a versatile and useful method of preparing aryl amine derivatives which are important to a diverse array of fields such as natural products, pharmaceuticals, dendrimers, polymers, organic materials etc.[13-14]

II. Materials &Methods:

Melting points were determined by open capillary tubes, and are uncorrected. The ^{1}H NMR, ^{13}C NMR were recorded in the indicated solvent on a Varian 300 MHz &100 MHz spectrometer with TMS as an internal standard. All chemical shifts (δ) were reported in ppm. IR spectra (KBr pellet) were recorded on a Perkin Elmer BX series FT-IR spectrometer and mass spectra were measured on a GC/MS-QP1000EX (EI,70eV) mass spectrometer. The progress of the reaction was monitored by thin layer chromatography Elemental analyses were performed on a PerkinElmer 240 CHN analyzer.

III. Results and Discussion:

The present investigation reports the synthesis of new 1-(5-isopropoxy-2-methyl-4-nitrophenyl)-1*H*-benzo[*d*] imidazole derivatives(4a-j) by the coupling between 1-Chloro-5-isopropoxy-2-methyl-4-nitrobenzene(2) and substituted benzimidazole (3) by using palladium-based heterogeneous catalyst is "Tris (dibenzylidine acetone) di palladium" named as Buchwald and Hartwig coupling and it involves in the C-N cross-coupling like amination of aryl halide and benzimidazole. In recent years the scope of metal–mediated cross–coupling has expanded immensely, with carbon–nitrogen cross–coupling emerging to the forefront as a versatile and useful method of preparing aryl amine derivatives, C-C and C-N coupling reactions have become an effective tool to develop environmentally friendly and economically sound manufacturing processes in a shorter time period. Buchwald-Hartwig aminations has been one of the remarkable topics in the reaction research area.

The data revealed that the compounds 4c, 4e, 4g and 4f have showed excellent antibacterial activity against the test bacteria and nearly equal to the standard drug. Compounds 4b, 4d and 4i have showed moderate to activity where as the remaining showed least activity. The structures of newly synthesized and characterized

by melting points, TLC, compounds have been established by elemental analysis, and IR, NMR & Mass spectral data

Scheme:

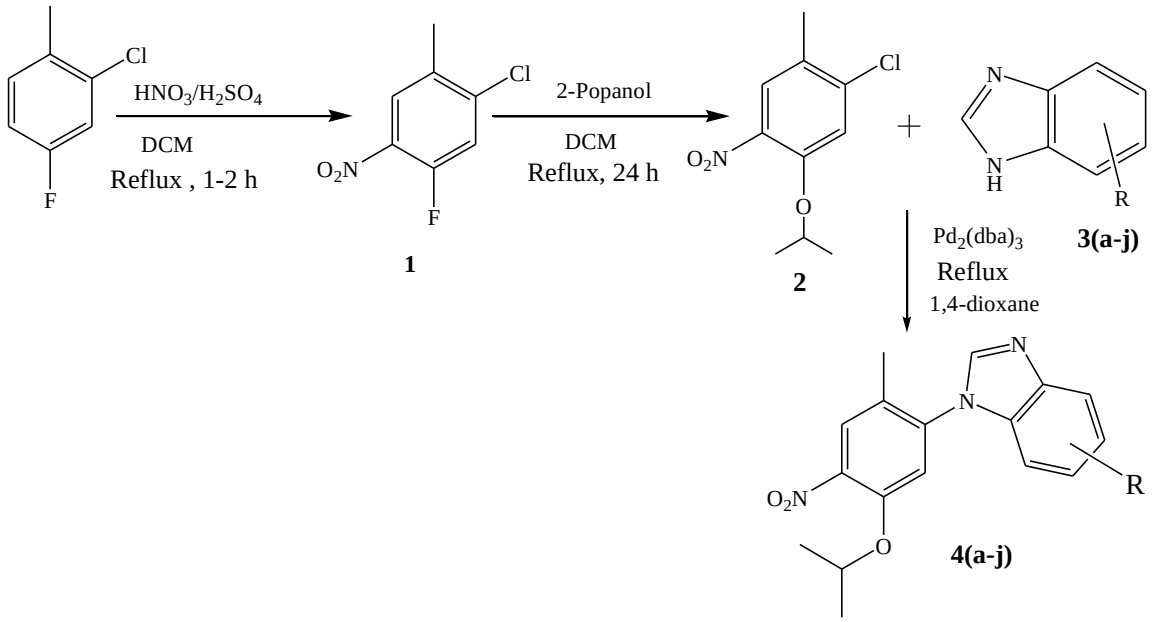

Table 1

compound	R	compound	R
a	H	f	2-chloro
b	6-chloro	g	Ethyl 2-caroxylate
c	6,7-dichloro	h	2-carbonylchloride
d	6-methyl	i	6-methoxy
e	6,7-dimethyl	j	5-hydroxy

Synthesis of 1-Chloro-5-fluoro-2-methyl-4-nitrobenzene (1)

2-Chloro-4-fluoro-1-methylbenzene (0.01 mmol) was added to a stirring mixture of nitric acid (0.01 m mol), and DCM (10 mL), was added drop wise. The flask was equipped with a water condenser fitted with a calcium chloride guard tube and the reaction was heated at 70 °C for 1 h. The reaction mixture was cooled to room temperature, analytical grade acetone (30 mL) was then added and the mixture was stirred for 5 min. The product was extracted by recrystalisation from acetone.

Synthesis of 1-Chloro-5-isopropoxy-2-methyl-4-nitrobenzene (2)

Under an atmosphere of dry nitrogen, potassium hydroxide (0.01 mmol) was added to a solution of 1-Chloro-5-fluoro-2-methyl-4-nitrobenzene (0.01 mmol) and 2-propanol (0.011 mmole) in DCM (20 ml) and the mixture was stirred at reflux temperature for 24 h. Dilute HCl was added until the solution was pH^1 and the mixture was continuously extracted with dichloromethane, dried ($MgSO_4$), and evaporated to yield crude material. Column chromatography, using dichloromethane as the eluent, gave product.

Synthesis of 1*H*-benzo[d]imidazole (3a)

In a 500-cc. round-bottomed flask (0.5 mole) of *o*-phenylene diamine is treated with (0.75mol) of formic acid. The mixture is heated in a water bath at 100°C for 2h. After cooling, 10% sodium hydroxide solution is added slowly, with thorough mixing by rotation of the flask, until the mixture is just alkaline to litmus. The crude benzimidazole is collected with suction in a 75-mm. Büchner funnel ice-cold water is used to rinse all solid out of the reaction flask to afford the compound (3). A similar procedure was used to synthesized different derivatives (3b-j) with slight modifications at reaction conditions

1-(5-isopropoxy-2-methyl-4-nitrophenyl)-1*H*-benzo[d]imidazole derivatives (4a)

A round-bottomed flask was charged with $Pd_2(dba)_3$ (5 mol %), 1-Chloro-5-isopropoxy-2-methyl-4-nitrobenzene (0.01 m mol), appropriate benzimidazole (0.01 m mol), Cs_2CO_3 (1.5 m mol) and dry 1,4-dioxane (5 ml). The flask was flushed with argon for 5 min. The mixture was heated at reflux under magnetic stirring. After cooling down to room temperature, the reaction mixture was concentrated and the residue was purified by flash column chromatography on silica gel.

1-(5-Isopropoxy-2-methyl-4-nitrophenyl)-1*H*-benzo[*d*]imidazole (4a)

M.P(226^{0}C);Yield 83%; IR: (KBr) λ_{max}(cm^{-1}): 3136 (N-H,benzimidazole);836(C-O);1684(C=N); ^{1}H NMR (300 MHz, DMSO): δ = 1.41 (d, 6H,2(-CH_3)), 2.36 (s, 3H,-CH_3), 4.61 (m, 1H,-CH), 7.10(s,1H,ArH),7.50(m,4H,ArH),7.71(s,1H,ArH),8.01(s,1H,ArH);^{13}CNMR(100MHz, DMSO): δ=19.03,21.80,73.36,110.21,110.23,114.10,117.10,119.85,125.05,127.20,128.30,131.02,136.01,142.10and150.02;Mass:m/z=326[M^{+1}];Anal.Calcd.For:$C_{17}H_{17}N_3O_3$;C, 65.58; H, 5.50; N, 13.50; Found:C,65.32;H,5.26;N,13.29

1-(5-Isopropoxy-2-methyl-4-nitrophenyl)-6-chloro-1*H*-benzo[*d*]imidazole (4b)

M.P(228^{0}C);Yield 81%;IR:(KBr)λ_{max}(cm^{-1}):3134(N-H, benzimidazole);834(C-O);1682(C=N);^{1}H NMR (300 MHz, DMSO): δ = 1.40 (d, 6H,2(-CH_3)), 2.38 (s, 3H,-CH_3), 4.62 (m, 1H,-CH), 7.11 (s, 1H,ArH), 7.53 (m, 3H,ArH), 7.72 (s, 1H,ArH), 8.02 (s, 1H,ArH);Mass: m/z=347 [M^{+1}]; Anal.Calcd.For:$C_{17}H_{16}ClN_3O_3$;C, 59.05; H, 4.66; N, 12.15; Found:C,58.81;H,4.33;N,11.85

6,7-Dichloro-1-(5-isopropoxy-2-methyl-4-nitrophenyl)-1*H*-benzo[*d*]imidazole(4c)

M.P (230^{0}C); Yield 80%; IR: (KBr) λ_{max}(cm^{-1}): 3132 (N-H, benzimidazole);830(C-O);1681(C=N);^{1}H NMR (300 MHz, DMSO): δ = 1.43 (d, 6H,2(-CH_3)),2.35(s, 3H,-CH_3,4.63 (m, 1H,-CH),7.09 (s,1H,ArH), 7.22 (s, 1H,ArH), 7.43 (s, 1H,ArH), 7.73 (s, 1H,ArH), 8.03 (s, 1H,ArH);Mass: m/z=381[M^{+1}]Anal.Calcd.For:$C_{17}H_{15}ClN_3O_3$;C, 53.70; H, 3.98; N, 11.05; Found:C,53.49;H,3.63;N,10.75

1-(5-Isopropoxy-2-methyl-4-nitrophenyl)-6-methyl-1*H*-benzo[*d*]imidazole (4d)

M.P(224^{0}C);Yield 78%; IR: (KBr) λ_{max}(cm^{-1}): 3130(N-H, benzimidazole);832(C-O);1680(C=N); ^{1}H NMR (300 MHz, DMSO): δ = 1.42 (d, 6H,2(-CH_3)), 2.31 (s, 3H,-CH_3), 2.37 (s, 3H,-CH_3), 4.61(m, 1H,-CH),7.10 (s,1H,ArH),7.48 (m, 3H,ArH), 7.72 (s, 1H,ArH), 8.02 (s, 1H,ArH);Mass: m/z=326[M^{+1}];Anal.Calcd.For:$C_{18}H_{19}N_3O_3$;C,66.45;H,5.89;N,12.91;Found:C,66.20;H,5.41;N,12.61

1-(5-Isopropoxy-2-methyl-4-nitrophenyl)-6,7-methyl-1*H*-benzo[*d*]imidazole(4e)

M.P(228^{0}C);Yield76%;IR:(KBr)λ_{max}(cm^{-1}): 3129(N-H, benzimidazole);831(C-O);1679(C=N);^{1}H NMR (300 MHz, DMSO): δ = 1.43 (d, 6H,2(-CH_3)), 2.32 (s, 6H,2(-CH_3)), 2.36 (s, 3H,-CH_3), 4.63(m,1H,-CH),7.08(s,1H,ArH),7.19(s,1H,ArH),7.50(s,1H,ArH),7.74(s,1H,ArH), 8.04 (s,1H, ArH);Mass:m/z=340[M^{+1}];Anal.Calcd.For:$C_{19}H_{21}N_3O_3$;C,67.24;H,6.24;N,12.38;Found:C,66.95;H,6.00; N,12.06

2-Chloro-1-(5-isopropoxy-2-methyl-4-nitrophenyl)-1*H*-benzo[*d*]imidazole (4f)

M.P(220^{0}C);Yield78%;IR:(KBr)λ_{max}(cm^{-1}):3131 (N-H, benzimidazole);833(C-O);1678(C=N);^{1}H NMR (300 MHz, DMSO): δ = 1.40 (d, 6H,2(-CH_3)), 2.34 (s, 3H,-CH_3), 4.60 (m, 1H,-CH), 7.11 (s,1H,ArH),7.53(m,4H,ArH),7.72(s,1H,ArH);Mass:m/z=347[M^{+1}];Anal.Calcd.For:$C_{17}H_{16}ClN_3O_3$;C,59.05;H,4.66;N,12.15; Found:C,18.72;H,4.35;N,11.89

Ethyl 1-(5-isopropoxy-2-methyl-4-nitrophenyl)-1*H*-benzo[*d*]imidazole-2-carboxylate (4g)

M.P(224^{0}C);Yield75%;IR:(KBr)λ_{max}(cm^{-1}):3134 (N-H, benzimidazole);832(C-O);1680(C=N);^{1}H NMR (300 MHz, DMSO): δ = 1.22 (t, 3H,-CH_3), 1.43 (d, 6H,2(-CH_3)), 2.33 (s, 3H,-CH_3), 4.02 (q, 2H-CH_2), 4.63 (m, 1H,-CH), 7.09 (s, 1H,ArH), 7.52 (m, 4H,ArH), 7.71 (s, 1H,ArH);Mass: m/z=384[M^{+1}];Anal.Calcd.For:$C_{20}H_{21}N_3O_5$;C,62.65;H,5.52;N,10.96;Found:C,62.28;H,5.20;N,10

1-(5-Isopropoxy-2-methyl-4-nitrophenyl)-1*H*-benzo[*d*]imidazole-2-carbonylchloride (4h)

M.P(230^{0}C); Yield 76%; IR: (KBr) λ_{max}(cm^{-1}): 3132 (N-H, benzimidazole);832(C-O);1681(C=N);^{1}H NMR (300 MHz, DMSO): δ = 1.40 (d, 6H,2(-CH_3)), 2.34 (s, 3H,-CH_3), 4.60 (m, 1H,-CH), 7.10 (s, 1H,ArH), 7.53 (m, 4H,ArH), 7.72 (s, 1H,ArH);Mass: m/z=375 [M$^+$];Anal.Calcd.For:$C_{18}H_{16}ClN_3O_4$;C,57.84;H,4.31;N,11.24; Found:C,57.62;H,4.03;N,10.96

1-(5-Isopropoxy-2-methyl-4-nitrophenyl)-6-methoxy-1*H*-benzo[*d*]imidazole (4i)

M.P (228^{0}C); Yield 78%; IR: (KBr) λ_{max}(cm^{-1}): 3128 (N-H, benzimidazole);835(C-O);1679 (C=N);^{1}H NMR (300 MHz, DMSO): δ = 1.42 (d, 6H,2(-CH_3)), 2.33 (s, 3H,-CH_3), 3.78 (s, 3H,-CH_3), 4.64 (m, 1H,-CH), 7.11 (s, 1H,ArH),7.52 (m, 4H,ArH), 7.71 (s, 1H,ArH);Mass: m/z=342[M^{+1}];Anal.Calcd.For:$C_{18}H_{19}N_3O_4$;C,63.33;H,5.61;N,12.31;Found:C,63.05;H,5.29;N,12

3-(5-Isopropoxy-2-methyl-4-nitrophenyl)-3*H*-benzo[*d*]imidazol-5-ol (4j)

M.P(226^{0}C); Yield 80%; IR: (KBr) λ_{max}(cm^{-1}): 3135 (N-H, benzimidazole);834(C-O);1681(C=N); ^{1}H NMR (300 MHz, DMSO): δ = 1.43 (d, 6H,2(-CH_3)), 2.32 (s, 3H,-CH_3), 4.62 (m, 1H,-CH), 7.10 (s, 1H,ArH), 7.55(m, 3H,ArH), 7.73 (s, 1H,ArH), 8.03 (s, 1H,ArH), 9.81 (brs, 1H,-OH);Mass: m/z=328 [M^{+1}];Anal.Calcd.For:$C_{17}H_{17}N_3O_4$;C,62.38; H, 5.23; N, 12.84; Found:C,62.10;H,4.95;N,12.67.

Anti bacterial activity

Anti bacterial activity by well diffusion method

The antibacterial activity of synthesized compounds was evaluated against nine bacteria by using well diffusion method. Gentamycin sulfate was employed as standard drug to compare the results.

Culture medium

Strains of *M.tuberculosis, M.luteus, MRSA,Bacillus subtilis, Bacillus cereus, E.Coli Salmonella typhi, P.aurgenosa,P.vaulgaris* were taken from department of microbiology, Kakatiya University Warangal. The bacterial cultures were developed by selective nutrient broth at 37°C and stored at 4°Cfor further use.Nutrient broth was used for the preparation of inoculums of the bacteria and nutrient agar was used for the screening method[15]. A reference standard for test bacteria was made by dissolving accurately weighed quantity of Gentamycin sulfate in sterile distilled water. All the newly synthesized ten compounds have been evaluated for antibacterial activity against test bacteria. The results are compared with Gentamycin sulfate. The anti bacterial results were tabulated in table2.

TABLE2 :ANTIBACTERIAL ACTIVITY OF COMPOUNDS (4a-j)

			Gram positive				**Gram negative**			
comp	conc.	M.tuber	M.luteus	MRSA	B.Subtilis	B.Cereus	P.aurgen	E.Coli	P.vulgaris	S.typi
4a	50	14	13	15	13	12	12	15	13	10
	100	16	15	17	13	13	13	15	15	12
4b	50	15	14	17	14	15	13	16	14	12
	100	15	16	19	16	15	15	17	16	13
4c	50	17	16	20	20	19	15	19	18	15
	100	19	16	22	21	20	16	20	19	17
4d	50	16	15	18	17	16	14	17	15	13
	100	18	16	20	18	20	15	19	17	14
4e	50	20	19	24	52	16	17	24	22	20
	100	23	22	26	26	18	19	26	23	22
4f	50	18	18	22	23	22	16	21	20	19
	100	22	20	25	25	24	17	23	21	21
4g	50	22	12	25	26	20	16	25	23	22
	100	25	13	27	28	24	18	27	25	24
4h	50	15	13	15	15	22	25	13	12	10
	100	16	14	17	17	23	27	15	14	12
4i	50	15	10	16	16	13	15	15	14	8
	100	17	12	19	17	15	17	16	15	10
4j	50	12	12	11	10	9	8	13	10	12
	100	14	15	12	12	11	10	16	12	14
CHP	50	25	26	27	25	26	20	28	25	23
	100	27	28	30	28	28	22	29	27	25

IV. Conclusion:

The present study reports an efficient synthesis of compounds 4 (a-j) were according to C-N cross coupling by Buchwald-Hartwig method and the titled compounds were in appreciable yield.

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