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Nickel Catalyzed Synthesis of *N*-aryl and *N*-heteroaryl Substituted Benzene Sulphonamides and their Biological Activity Evaluation

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Abstract

The synthesis of various *N*-aryl and *N*-heteroaryl substituted benzene sulphonamide 4a-e is reported. The intermediate benzene sulphonamide 2 was obtained by the reaction of benzene sulphonyl chloride 1 with ammonium hydroxide. The coupling reaction of the benzene sulphonamide 2 with various aryl halides and heteroaryl halides 3a-e via tandem catalysis gave the *N*-aryl and *N*-heteroaryl benzene sulphonamide derivatives 4a-e. The compounds were characterized using FTIR, ^{1}HNMR and ^{13}CNMR. These sulphonamides 2 and 4a-e were tested for antibacterial activities against *Staphylococcus aureus, Enterococcus faecalis, Salmonella typhi, Klebsiella pneumonia, Pseudomonas aeruginosa,* and *Escherichia coli.* The antifungal activities were tested against *Candida albican and Aspergillus niger* using Agar cup diffusion technique. Some of the tested compounds showed significant antimicrobial activities with improved potency after arylation, though none of the sulphonamides was as active as standard tetracycline and ketoconazole for antibacterial and antifungal activities respectively.

Keywords: *N*-aryl sulphonamides; Antibacterial; Antifungal; Buchwald-Hartwig protocol; Nickel catalysis; Spectroscopy

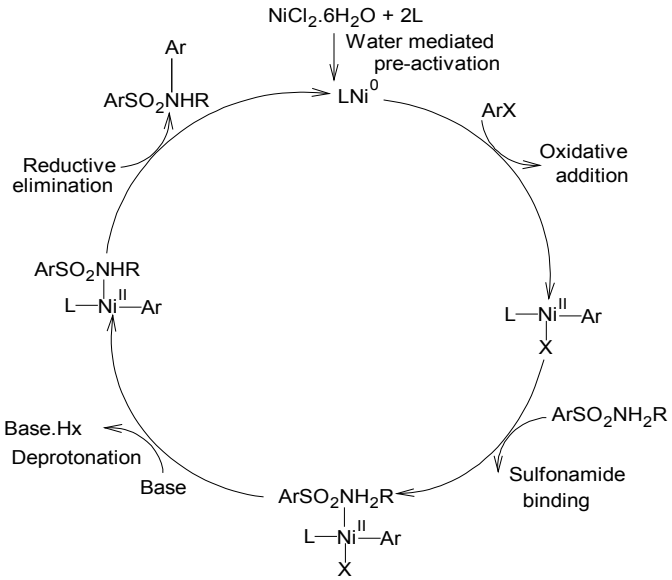
Introduction

Sulphonamides were the first efficient treatment to be employed systematically for the prevention and cure of bacterial infections [1]. Mechanistically, sulphonamides act as antimetabolites. They compete for incorporation with *p*-amino benzoic acid into folic acid. This principle introduced and sustained the concept of selective antagonism. Sulphonamides are widely used in medicinal chemistry because of their low cost, low toxicity and excellent biological activities. Many infectious diseases caused by bacteria are cured by widely use of sulphonamides [2]. In addition to their use as antibacterial agent, sulphonamides are widely used as antidiuretics [3], anti-convulscant [4], anticancer [5], anti-retroviral [6], anti-hypertensive [7], anti-malarial [8], and anti-diabetic agent [9]. Aziz-Ur-Rehman et al. [10] reported that various *N*-substituted derivatives of benzene sulphonamides had acetyl cholinesterase, butyryl cholinesterase and lipoxygenase activities. Subhakara et al. [11] has reported sulphonamides derived from C-8 alkyl chain of anacardic acid mixture isolated from cashew nut shell liquid to possess fascinating antibacterial activity. Sorbera et al. [12] reported Pazopanib Hydrochloride containing a sulphonamide moiety as a potent and selective multi-targeted receptor of tyrosine kinase that blocks tumour growth and inhibits angiogenesis. Fors et al. [13] successfully used a new biarylphospine ligand (t-Bu Brettphos) for palladium catalyzed cross coupling reactions of 1-chloro-2-methylbenzene and acetamide to produce *N*-phenylacetamide. They reported that this system shows the highest turnover to date for these reactions, especially for aryl chloride substrates bearing an ortho substituent.

Palladium catalyzed reaction has been one of the most widely used protocol for C-N moiety formation in organic synthesis. On the other hand, Ni catalyzed amidation reactions have received less attention. At present, there is little report of nickel catalyzed tandem reactions for the formation of C-N moiety in compounds. It is the interest in this direction that prompted the present synthesis of benzene sulphonamide derivatives preferentially based on cheap Ni (11) precursor, suitable ligand and a mild reducing agent using the Buchwald-Hartwig protocol.

The Buchwald-Hartwig amidation protocol is able to connect highly functionalized components and is compatible with a wide variety of functional group. This generality makes it well suited for the construction of a body of amide analogues from a common intermediate [14]. Below is a sketch of proposed catalytic C-N coupling (Scheme 1).

The simplified catalytic cycle consists of three elementary steps-oxidative addition of Ar-x onto the metal center, transmetallation to



Scheme 1: proposed catalytic cycle for C-N coupling.

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produce organo-metal intermediates and reductive elimination to form cross coupling products and to regenerate the active catalysts. Throughout the cycles, the catalyst is profoundly influenced by the steric and electronic properties of these ligands [15]. In the present work, we wish to report the synthesis, spectroscopic characterization and antimicrobial activities of novel nickel catalyzed *N*-aryl and *N*-heteroaryl substituted benzene sulphonamides.

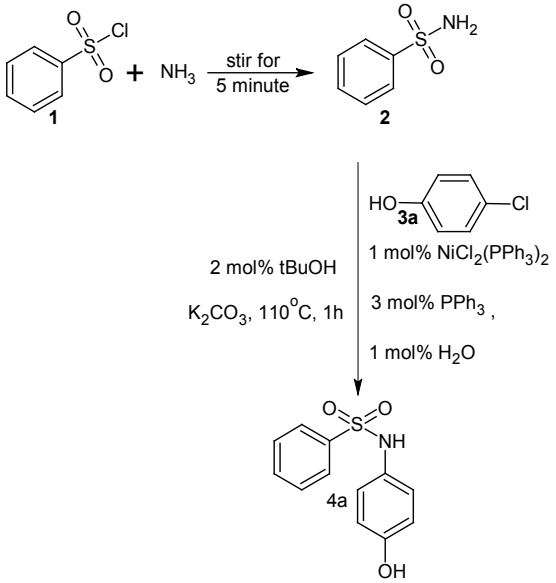
Material and Methods

Chemistry

All reactions including the pre-activation of the nickel (11) salt were carried out under an atmosphere of nitrogen. Also, the reagents were of analytical grade and purchased from Sigma-Aldrich and BDH. Column chromatography was carried out using Merck silica gel adsorbent 230-400 mesh. Melting points were determined with Fischer John's melting point apparatus and are uncorrected. IR spectra were recorded on 8400s Fourier Transform Infrared (FTIR) spectrophotometer at National Research Institute for Chemical Technology (NARICT), Zaria, Kaduna state and recorded in wave number. Nuclear Magnetic Resonance (^{1}H-NMR and ^{13}C-NMR) were determined using Varian 400 MHz at Strathclyde University Scotland. Chemical shifts were reported in (δ) scale.

Synthesis

Benzene sulphonamide (2): Using a 100 mL Erlenmeyer flask, ammonium hydroxide (2.10 g, 60 mmol) was added to benzene sulphonyl chloride (5.31 g, 30 mmol) and stirred for 5 minutes, after which 10 mL of distilled water was added and stirring continued for 3 minutes, the mixture was then heated at 60°C using water bath for 2 minutes. It was allowed to cool, and then chilled in ice-water. The solid product was filtered via suction filtration. It was air dried and recrystallized from a 1:1 mixture of water and ethanol to give a glistering white crystalline solid, benzene sulphonamide 2. Yield 3.67 g, (78%), m.p 148-149°C IR (KBr) cm^{-1} 3400, 3380 (NH_2), 3040 (CH aromatic), 1580, 1460 (C=C aromatic), 1120 and 1090 (SO_2). ^{1}HNMR (400MHz, DMSO-d_6) δ: 3.5 (s, 2H), 7.37 (s, 1H), 7.58 (m, 2H), 7.58 (m, 2H) (Scheme 2).



Scheme 2: Synthetic pathway of *N*-aryl and *N*-heteroaryl benzene sulphonamide.

Bis (Triphenylphospine) nickel (11) chloride: This complex compound was prepared according to the procedure developed by LM Venanzi [16]. A salt of nickel (11) chloride hexahydrate (2.38 g, 10 mmol) was dissolved in water (2 mL) and diluted with glacial acetic acid (50 mL) and mixed with triphenylphospine (5.25 g, 20 mmol) dissolved in glacial acetic acid (25 mL). The olive green microcrystalline precipitate was kept in contact in the solution of glacial acetic acid for 24 h to give a dark blue crystal which was filtered using suction. The complex was washed with glacial acetic acid and dried in a desiccator.

General procedure for derivatives (4a-e)

Bis (triphenylphospine) nickel (11) chloride (6.54 g, 10 mmol) and triphenylphospine (5.25 g, 30 mmol) were both added into a 50 mL flask. The solvent (*t*-butanol (4 mL) and distilled water (2 mL)) was introduced using a syringe and the mixture stirred for 10 min at room temperature under nitrogen atmosphere. Afterward, it was heated at 80°C for 1.5 min. Benzene sulphonamide (2) (1.41 g, 10 mmol), K_2CO_3 (1.38 g, 10 mmol) and substituted heteroaryl and aryl halides were added to the mixture with the solvent *t*-butanol and water in the ratio of 2:1 under inert atmosphere. The mixture was refluxed for 1h at 100-110°C with stirring. The mixture was then cooled to room temperature, diluted with ethyl acetate, washed with water and purified via column chromatography.

***N*-(4-Hydroxyphenyl) benzene sulphonamide (4a):** Using 2, bis (triphenylphospine) nickel (11) chloride, 4-chlorophenol **3a** and triphenylphospine as starting materials, the title compound 4a was obtained as a creamy white crystalline solid; Yield 1.78 g (79%), m.p. 126-127°C. IR (KBr) cm^{-1} 3347 (OH), 3258 (N-H), 3057 (aromatic C-H), 1568.18 (C=C aromatic), 1325 (C-N), 1164 (SO_2), 740 (C-S). ^{1}HNMR (400MHz, DMSO-d_6) δ: 3.4 (s, 1H), 7.24 (m, 2H), 7.39 (m, 5H), 7.57 (q, J=5.69Hz, 2H), δ7.85 (m, 1H).

^{13}CNMR (400MHz, DMSO-d_6), δ: 144.74, 137.30, 137.20, 133.92, 133.73, 132.33, 129.57, 129.49, 129.40, 129.32 and 126.14

***N*-(2, 6H-diaminopyrimidin-4-yl) benzene sulphonamide (4b):** Using 2, bis (triphenylphospine) nickel (11) chloride, 4-chloro-2,6-diaminopyrimidine 3b and triphenylphospine as starting materials, the title compound 4b was obtained as a white crystalline solid; Yield 1.98 g, (83%) m.p. 123-124°C IR (KBr) cm^{-1} 3401.58 (N-H), 1569.14(C=C aromatic), 1303 (C-N), 1150.58 (SO_2). ^{1}HNMR (400MHz, DMSO-d_6) δ: 3.4(s, 1H), 5.7 (s, 1H), 6.33 (s, 2H), 6.59 (s, 2H), 7.32 (m, 1H), 7.58 (m, 2H), 7.83 (m, 2H).

***N*-(10H-phenothiazin-1-yl) benzene sulphonamide (4c):** Using 2, bis (triphenylphospine) nickel (11) chloride, 2-Chlorophenothiazine **3c** and triphenylphospine as starting materials, the title compound 4c was obtained as a grey crystalline solid; Yield 2.15 g, (68%) m.p. 187-188°C IR (KBr) cm^{-1} 3336.96 (N-H), 3069.81 (C-H aromatic),1576.86 (C=C aromatic), 1310.67 (C-N), 1145.75 (SO_2), 726.22 (C-S). ^{1}H-NMR (400MHz, DMSO-d_6) δ: 3.5 (s, 1H), 6.66 (dd, J_1=0.98Hz, J_2=7.92Hz, 1H), 6.70 (d, J=2.16Hz, 1H), 6.78 (m, 4H), 6.92 (d, J=8.08Hz, 2H), 7.01 (td, J=1.35Hz, J=7.72Hz), 8.76 (s, 1H). ^{13}CNMR (400MHz, DMSO-d_6) δ: 144.1, 141.7, 132.4, 128.4, 128.01, 126.90, 122.92, 121.77, 116.59, 116.1, 115.24, 114.29.

***N*-(4-aminophenyl) benzene sulphonamide (4d):** Using 2, bis (triphenylphospine) nickel (11) chloride, 2-bromoaniline **3d** and triphenylphospine as starting materials, the title compound 4d was obtained as a white crystalline solid; Yield 1.14 g, (51%) m.p. 142-143°C IR (KBr) cm^{-1} 3341.78 (NH), 3261.74 (NH), 3071.74 (C-H), 1568.18 (C=C aromatic), 1325.14 (C-N), 1157 (SO_2), 706.93 (C-S). ^{1}HNMR (400MHz, DMSO-d_6) δ: 3.5 (s, 3H), 7.24 (m, 2H), 7.39 (m, 2H), 7.58 (m, 4H), 7.84 (m, 1H).

***N*-(4-nitropyridin-2-yl) benzene sulphonamide (4e):** Using 2, bis (triphenylphospine) nickel (11) chloride, 2-chloro-5-nitropyridine **3e** and triphenylphospine as starting materials, the title compound 4e was obtained as a white crystalline solid, yield 2.22 g, (88%) m.p. 120-121°C IR (KBr) cm^{-1} 3332.14 (NH), 3078.49 (Ar-H), 1567.21 (C=C aromatic) 1452.45 (N=O), 1324.18 (C-N), 1150.58 (SO_2), 723.33 (C-S). ^{1}HNMR (400MHz, DMSO-d_6) δ: 7.24 (m, 1H), 7.39 (m, 2H), 7.84 (m, 1H), 8.63 (dd, J_1=2.86Hz, J_2=8.74Hz, 1H), 9.24 (d, J=2.86Hz, 1H).

Antimicrobial activity

Agar cup diffusion technique as described by Adeniyi and Odelola [17] was used to determine the antimicrobial activity of the synthesized compounds. Sensitivity test agar plates were seeded with 0.1 ml of overnight culture of microorganism. The seeded plates were allowed to set after which cups were made in each sector previously drawn on the backside of the bottom plate using marker. Using a sterile pipette, each cup was filled with six drops of their corresponding synthesized compound (20 mg/mL). The solubilizing solvent was DMF. All the plates were incubated at 37°C for 24h. Zones of clearance round each cup means inhibition and the diameter of such zones were measured. The graph of IZD^2 against the log of concentration was plotted for each plate containing a specific compound and a microorganism. The anti-log of the intercept on x-axis gives the MIC. The procedure was repeated for tetracycline (standard antibacterial agent), fluconazole (standard antifungal agent) and DMF (solvent).

Results and Discussion

We described here the synthesis of novel *N*-aryl and *N*-heteroaryl substituted benzene sulphonamides via Buchwald-Hartwig protocol and their biological activities using benzene sulphonyl chloride as starting material.

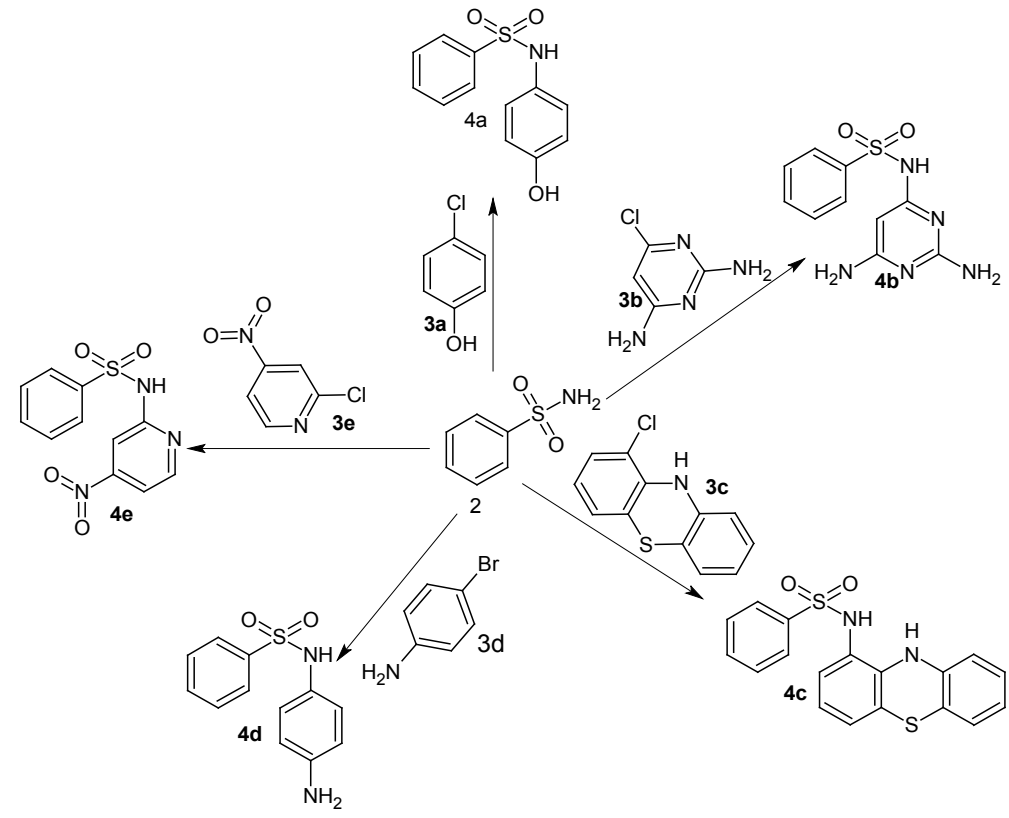
On stirring ammonium hydroxide with benzene sulphonyl chloride (1) for five min, benzene sulphonamide (2) was obtained as a white crystal. The water promoted activation of bis (triphenylphosphine) nickel (II) chloride is as shown below

$$NiCl_2(PPh_3)_2 + 2PPh_3 + H_2O \longrightarrow (Ph_3P)_2Ni(0) + O{=}PPh_3 + 2HCl$$

A mixture of bis (triphenylphosphine) nickel (11) chloride and triphenylphosphine in a solvent of *t*-butanol and water was pre-activated for 2 min at 80°C. Benzene sulphonamide (2), appropriate aryl chlorides or heteroaryl chloride (3a-e) and potassium carbonate were added with a further addition of *t*-butanol and water. On further stirring for about 1h at 110°C, the corresponding *N*-aryl and *N*-heteroaryl substituted benzene sulphonamides (4a-e) was obtained after purification using column chromatography. The structures of these compounds were determined using FTIR, ^{1}HNMR and ^{13}CNMR. The compounds 2 and 4a-e were screened for antimicrobial activity (Scheme 3).

Biological activity

The *N*-aryl and *N*-heteroaryl substituted benzene sulphonamides 4a-e were screened for their antibacterial and antifungal activities against some pathogenic bacteria viz. *Staphylococus aureus, Klebsiella pneumonia, Enterococus faecalis, Salmonella typhi, Pseudomonas aeruginosa, Escherichia coli* and *Aspergillus niger* and *Candida albican* respectively using agar cup diffusion method. The antibacterial activities of the *N*-aryl and *N*-heteroaryl 4a-e when compared with the intermediate 2 showed that the coupling improved the antibacterial



Scheme 3: Synthesis of various *N*-aryl **(4a and 4d)** and *N*-heteroaryl **(4b, 4c and 4e)** substituted Benzene sulphonamide.

Compound No	*S. aureus*	*K. pneumonia*	*S. typhi*	*P. aeruginosa*	*E. coli*	*E. faecalis*	*C. albican*	*A. niger*
2	+	+	+	+	+	+	+	250
4a	500	500	500	250	500	+	+	+
4b	+	500	500	250	500	500	100	500
4c	250	500	1000	500	+	+	+	+
4d	+	250	+	+	+	+	250	500
4e	500	500	+	+	500	100	+	+
K	+	+	+	+	+	+	62.5	125
T	15.63	62.50	125	62.50	31.25	31.25	+	+

+ imply no activity, K imply ketoconazole, T imply tetracycline

Table 1: Minimum Inhibitory Concentration (µg/mL).

activity given the fact that the intermediate was inactive against the tested bacteria but compounds 4a-e were very active though none of the novel sulphonamides were as active as the standard antibacterial agent tetracycline. The antifungal activity investigation showed that compounds 4a-e had improved activity when compared with the intermediate 2 even though as was the case of the antibacterial activity, none of the compounds were more active than the standard ketoconazole (Table 1).

Conclusion

In conclusion, the synthesis of benzene sulphonamide and its functionalized N-aryl and N-heteroaryl substituted analogues via Buchwald-Hartwig tandem amidation protocol was successful using cheap nickel catalyst. The synthetic route is quite economical given the use of cheap nickel in catalyzing the reaction. The assigned structures were supported by spectral analysis. The compounds synthesized were also screened against some pathogenic microbes of tropical interest and was found to possess interesting biological activity.

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