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PG/M.Sc/11/59560 |
| **Author 2**   |  |
| **Author 3**   |  |
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NICKEL CATALYZED SYNTHESIS OF N-ARYL AND N-HETEROARYL
SUBSTITUTED BENZENESULPHONAMIDE AND THEIR
ANTIMICROBIAL ACTIVITIES

BY

CHUKWURAH, D. THOMPSON
PG/M.Sc/11/59560

DEPARTMENT OF PURE AND INDUSTRIAL CHEMISTRY

UNIVERSITY OF NIGERIA, NSUKKA.

JUNE 22, 2013.
TITLE PAGE

UNIVERSITY OF NIGERIA, NSUKKA
FACULTY OF PHYSICAL SCIENCES
DEPARTMENT OF PURE AND INDUSTRIAL CHEMISTRY
CHM 592, RESEARCH (PROJECT)

NICKEL CATALYZED SYNTHESIS OF N-ARYL AND N-HETEROARYL
SUBSTITUTED BENZENE SULPHONAMIDES AND THEIR ANTIMICROBIAL
ACTIVITIES

A RESEARCH PROJECT SUBMITTED IN PARTIAL FULFILMENT OF THE
REQUIREMENT FOR THE AWARD OF MASTER OF SCIENCE (M.Sc)
DEGREE IN ORGANIC CHEMISTRY

BY

CHUKWURAH. D. THOMPSON
PG/M.Sc/11/59560

PROJECT SUPERVISOR: PROF. U. C. OKORO
This work has been approved by the Department of Pure and Industrial Chemistry, University of Nigeria, Nsukka.

PROF. U. C OKORO
Project Supervisor

PROF. P. O UKOHA
Head of Department

EXTERNAL EXAMINER

Date_________________________
CERTIFICATION

This is to certify that the research work titled “Nickel catalyzed synthesis of N-(aryl and heteroaryl) substituted benzene sulphonamides and their antimicrobial activities” was carried out by CHUKWURAH, THOMPSON. D. (PG/M.Sc/11/59560) and has been approved by the undersigned as having met the standard of the Department of Pure and Industrial Chemistry University of Nigeria, Nsukka submitted in partial fulfilment of the requirements for the award of M.Sc in Organic Chemistry.

PROF. U. C OKORO
Project Supervisor

PROF. P. O UKOHA
Head of Department

Date_________________________  Date_________________________
DEDICATION

Dedicated to my mother, Mrs Felicia Nkadi Chukwurah
ACKNOWLEDGEMENT

Father Almighty, I thank Thee for giving me the grace of Thee infinite Mercies throughout my M.Sc program.

I wish to express my gratitude to my supervisor Prof. U. C. Okoro, who carried out his work with so much love for it and in the process inspire others to do likewise. My appreciation also goes to my mother, who has stood like a solid rock behind me. Also, my thanks goes to my uncle Mr Uzo Chukwurah for his support and my brothers Emeka and Ike Chukwurah for their brotherly support too.

With love from Nsukka, my gratitude goes to my fiancée Miss Victoria Enyogai for her very warm support, my big sister Mrs Isioma Anumba and her children (Paige, Feichi, Udodi, Uche and Deabele) and my ever present uncle Mr Anthony Ofili.

I also wish to thank all my friends at UNN (Chinwe, Ogechi, David and Chinelo) for their support and cooperation.
ABSTRACT

The synthesis of various substituted derivatives of \(N\)-(aryl) and \(N\)-(hetero) substituted benzenesulphonamide is reported. The intermediate benzene sulphonamide was obtained by the reaction between benzenesulfonyl chloride and ammonium hydroxide. The benzene sulphonamide derivatives were obtained by coupling benzene sulphonamide with various halogeno aryl and heteroaryl substituted compounds via tandem catalysis. The structures of the synthesized compounds were assigned by spectroscopic methods.

The antibacterial and antifungal activities of the synthesized products were also evaluated against \textit{Staphylococcus aureus}, \textit{Enterococcus faecalis}, \textit{Salmonella typhi}, \textit{Klebsiella pneumonia}, \textit{Pseudomonas aeruginosa}, \textit{Escherichia coli}, \textit{Candida albican} and \textit{Aspergillus niger} respectively, using Agar dilution technique. Some of the tested compounds showed significant activities but no improved potency was observed when compared to the standard drugs used, Tetracycline and Ketoconazole. Also, all the synthesized benzenesulphonamide derivatives were inactive against \textit{Escherichia coli}. 
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LIST OF ABBREVIATIONS

APIs: Active pharmaceutical ingredients
COX: Cyclooxygenase
DHPS: Dihydropteroate synthetase
DMSO: Dimethyl sulfoxide
DNA: Deoxyribonucleic acid
IR: Infrared Spectroscopy
KBr: Potassium bromide
m-CPBA: meta-Chloroperoxybenzoic acid
NMR: Nuclear magnetic resonance
PABA: para-Aminobenzoic acid
PFP: Pentafluorophenyl
PPh₃: Triphenylphosphine
SAR: Structure-Activity Relationship
TEA: Triethylamine
TCP: Trichlorophenol
CHAPTER ONE

1.0 INTRODUCTION

Compounds containing sulfonyl groups (R-SO\textsubscript{2}-R\textsuperscript{1}) have long been a research focus as a result of their biological importance, chemical applications and some of the aryl sulphonamide derivatives are a common substructure class present in a large number of active pharmaceutical ingredients APIs\textsuperscript{1}. Sulphonamide derivatives occupy a unique position in the drug industry with their potent antibacterial activities\textsuperscript{2}. They have also been shown to exhibit antifungal\textsuperscript{3}, antineoplastic\textsuperscript{4}, and antiviral\textsuperscript{5} activity, considering this class of compounds a “privileged structure” in medicinal chemistry\textsuperscript{6}.

1.1 BACKGROUND OF STUDY

Sulphonamides are groups of compounds consisting of SO\textsubscript{2}-NH\textsubscript{2} functional groups that have biological importance as antimicrobial agents\textsuperscript{7,8}. The term sulphonamides are used as a generic name for derivatives of sulphanilamide 1.

\begin{center}
\includegraphics[width=0.2\textwidth]{sulphonamide.png}
\end{center}

The discovery of medicinal property of 1 can be categorized as serendipitous, because it came about as an offshoot of dyes industry in Germany. In 1935, 1 was identified by Domagk et al\textsuperscript{9} as the active metabolite of the red azo dye known as prontosil 4-[(2,4–diaminophenyl) azo]benzenesulphonamide 2. It does not possess any activity \textit{in vitro}; however it metabolizes \textit{in vivo} to give the active agent 1 where it can interfere with the process of bacterial DNA synthesis and act as potent antibacterial agent\textsuperscript{9}. 
The discovery of 1 as drugs is considered to be an epochal era by making possible a direct attack on microbial infection thus, their application on chemotherapy is so well known that the name ‘sulpha drug’ is widely used as a general name for 1 derivatives as therapeutic agent\textsuperscript{10}. Sulpha drugs are synthetic antimicrobial agents which are derivatives of 1 that inhibit folic acid biosynthesis. Thus, interfering with various folate derivatives that are co-enzymes in numerous critical biological processes like:

- the synthesis of thymidine and purines
- synthesis of several amino acids.

As a result of this interference, the misled enzymes construct a false molecule of folic acid which is not able to carry out the vital function of true folic acid 3. The action of 1 illustrates the principle of selective toxicity where some differences between mammalian cells and bacterial cells is exploited, thus their use introduced and substantiate the concept of metabolic antagonism\textsuperscript{11}. Animal cells are not able to synthesize 3 by themselves and so, must be obtained through the consumption of food.

In addition, most bacteria are not able to utilize folic acid of exogen origin, so they synthesize the folic acid necessary for vital functions by themselves. This is the differences between bacterial and animal cells and it is the reason behind the selective toxicity of 1.
1, whose structure is similar to the structure of PABA 4, competes with 4 for inclusion in the folic acid molecules.

![Chemical structures](image)

In short by taking the place of 4, it interferes with the biosynthesis of folic acid. As a result, the misled enzymes construct a false molecule of folic acid 5, which is not able to carry out the vital function of 3.

![Chemical structures](image)

Thus 1 are bacteriostatic drugs that inhibit bacterial growth by interfering with the microbial synthesis of folic acid which by targeting DHPS enzyme that catalyzes folic acid pathway in bacteria and some eukaryotic cells but not present in human cell allows them to be considered as anti-metabolites.

The SAR of 1 shows how important their resemblance to 4 is to their activity. 1 all have the same nucleus to which various functional groups have added to the sulfonamido group 7 or which various substitution on the amino group N are made. These changes produce compounds with varying physical, chemical, pharmacological and antibacterial properties.
SAR shows the relationship between chemical structure of an agent and its biological activity\textsuperscript{11}. It also demonstrates the concept of how slight changes in the molecular structure of an agent can have tremendous effects on biological activities.

The syntheses of a large number of I analogue have led to the following conclusions\textsuperscript{10}.

\begin{itemize}
  \item The p-amino group N\textsubscript{4} is essential for activity and must be unsubstituted (i.e. R\textsubscript{1} = H). The only exception is when R = acyl (i.e. amides). The amides themselves are inactive but can be metabolized in the body to regenerate the active compound. Thus amides can be used as sulfonamide prodrugs\textsuperscript{27}.
  \end{itemize}

\begin{equation}
\text{Ac} - \text{NH} \quad \begin{array}{c}
\text{S} \\
\text{O} \\
\text{NHR} _2
\end{array} \quad \rightarrow \quad \begin{array}{c}
\text{H}_2 \text{N} \\
\text{S} \\
\text{O} \\
\text{NHR} _2
\end{array}
\end{equation}

\begin{itemize}
  \item The aromatic ring and the sulfonamide functional group are both required.
  \item The aromatic ring must be para-substituted only.
  \item The sulfonamide nitrogen N\textsubscript{1} must be secondary.
  \item R\textsubscript{2} is the only possible site that can be varied in sulfonamides.
\end{itemize}

R\textsubscript{2} can be varied by incorporating a large range of heterocyclic or aromatic structures which affects the extent to which the drug binds to plasma protein. This in turn controls the blood levels of the drug such that it can be short acting or long acting. Thus, a drug which binds strongly to plasma protein will be slowly released into the blood circulation and will be longer lasting. Varying R\textsubscript{2} can affect the solubility of I or the extent to which they bind to plasma protein. These variations are therefore affecting the pharmacodynamics of the drug, rather than its mechanism of action\textsuperscript{10}.

**CLASSIFICATION OF SULPHONAMIDE**

Classification of sulphonamides that is based on rate of absorption and half-life appears to be clinically relevant. Based on this the sulphonamides are classified into three groups\textsuperscript{14}.
**Short Acting:** Sulphonamides are considered short acting if the blood concentration levels remain higher than 50 g/mL for less than 12 h after a single therapeutic dose. They have been preferred for systemic infections as they are rapidly absorbed and rapidly excreted. Some examples of sulphonamides with short acting character are sulphisoxazole 10 and sulphathiazole 11 among others.

![Chemical structures of sulphisoxazole (10) and sulphathiazole (11)](image)

**Intermediate Acting:** Sulphonamides are considered intermediate acting if the blood plasma levels concentration of higher than 50 g/ml are obtained between 12 and 24 h. They have been used for infections requiring prolonged treatment. For instance, sulphamethoxazole 12 in combination with trimethoprim 13 commonly known as septran has been used for various infections such as recurrent urinary tract infections and it is especially active against invasive aspergillosis in AIDS patients.

![Chemical structures of sulphamethoxazole (12) and trimethoprim (13)](image)

**Long Acting:** Sulphonamides are considered long acting if the blood plasma levels concentration of higher than 50 g/ml are obtained 24 h after dosage. They are rapidly absorbed and slowly excreted. Example is sulfadimethoxine which is being used for the treatment of ulceration colitis.
In the late 1940s, penicillin began to replace the sulphonamides in chemotherapy due to its toxicity and because of suphonamide-resistant bacterial strains was becoming an increasing problem the result of indiscriminate use worldwide\textsuperscript{12}. However, sulphonamide are still being widely used in clinical practice even six decades after their discovery because the chemistry of sulphonamide has shown them to be highly efficient precursor in the preparation of various valuable biologically active compounds\textsuperscript{16} thus, providing wide choice of chemically modified 1 prepared to achieve safety (reduce toxicity, side effect) alter it spectrum of activity and potency\textsuperscript{17}. Also, the relative cheapness of the 1 is one of their most attractive features and accounts of much of their persistence in the market\textsuperscript{18}.

Sulfa drugs are still widely used against emerging infective diseases and to prevent infections in patient with weaken immune systems including patient integrating chemotherapy. The growing problem of antibiotic resistance has prompted renewed interest in sulpho drugs as a possible source of new therapeutic targets since it is free of super infection of problems caused by antibiotics\textsuperscript{19}.

Sulphonamides as a synthetic antibacterial agent have also had a strong impact on development in synthetic and medicinal chemistry which influenced later work in drug research in general and chemotherapy in particular. When pharmacokinetic studies became integral part of drug development, carefully observed side effects in pharmacological and clinical studies of the sulphonamide reveal new and unanticipated activities; successful exploitation of these leads opened up new areas in chemotherapy, such as oral anti-diabetics, carbonic anhydrase inhibitors and diuretics. This also highlighted the important of side effects of drugs as a source of new leads of side effect\textsuperscript{19}.
Thus, apart from the commercialized application as antimicrobial agents, various sulphonamides are also known to inhibit several enzymes such as carbonic anhydrase, cysteine protease, HIV protease and cyclooxygenase\(^{20}\). This was the beginning of extensive structure-activity correlations, which led to some valuable drugs during a short period of time: the carbonic anhydrase inhibitor acetazolamide 15 (Clinically being used for over 45 years), the widely used diuretic furosemide 16, the anticancer sulphonamide E7070 17 and HIV protease inhibitor amprenavir 18 (used for the treatment of Aids and HIV infections) cyclooxgenase (COX) inhibitor celecoxib 19 (treatment of osteoarthritis and rheumatoid arthritis.)
BUCHWALD-HARTWIG AMIDATION

Due to the ubiquity of N-arylamides in biologically active molecules, the development of efficient methods for their synthesis has been an active area of research for many years. The Goldberg-modified Ullman reaction was the first cross-coupling protocol to synthesize these compounds effectively from aryl iodides and amides using a stoichiometric quantity of copper\(^{21}\).

With most methods (Goldberg reaction nucleophilic aromatic substitution suffering from limited substrate scope and functional group tolerance, Buchwald\(^{22}\) and Hartwig\(^{23}\) develop user-friendly palladium-mediated methods for C(aryl)-N bond formation.

![Scheme II](image)

**Scheme II** Pd mediated process for C-N bond formation

The development of Buchwald-Hartwig reaction allowed for a facile synthesis and significantly expanded the repertoire of possible C-N bond formation.

The Buchwald-Hartwig Amidation reaction is a direct Pd or Ni catalyzed carbon-nitrogen bond formation between aryl halides and an amide in the presence of a stoichiometric amount of base, ligand and a solvent.

![Scheme III](image)

**Scheme III** Pd/Ni mediated amidation reaction

Amides is a generic representation of three classes of organic compounds-carbonic amides (-CONH\(_2\)), sulphonamide (-SO\(_2\)NH\(_2\)) and phosphoramide (-PO\(_2\)NH\(_2\)).

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. Below is a sketch of proposed catalytic C-N coupling

Scheme IV proposed catalytic cycle for C-N coupling

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

A Buchwald-Hartwig amidation usually require a catalytic system containing four components to efficiently generate and greatly influence the performance of a desired C-N bond coupling reaction.

**Ligands:** A transition metal catalyst can catalyze cross coupling reactions without additional supporting ligands, but usually only with reactive substrates (ArI) and a high temperature. The ligand serves to stabilize the transition metal intermediate, solubilize the...
catalyst and increase the rate of oxidative addition. Triphenylphosphine ligand is the most commonly used to give water-soluble catalyst systems for aqueous-phase cross coupling.\textsuperscript{26}

**Base:** A base is required to deprotonate the amide substrate prior to or after co-ordination to the transition metal centre. It should be noted that a highly active catalyst especially water mediated preactivation with phosphine ligands, allows a combination of weaker bases, thus rendering the procedure to be highly tolerant to a wider range of functional group.\textsuperscript{27}

**Solvent:** Buchwald- Hartwig amidation are usually run within an organic solvent system. The role of the solvent is two-fold. It dissolved the coupling partners as well as parts of the base and allowing for a respective temperature window for the reaction, the solvent also plays a crucial roles in stabilizing intermediates in the catalytic cycle.\textsuperscript{25}

**A nickel precursor:** Nickel catalyzed C-N bond forming reactions have become important and powerful tools in organic synthesis during the past decades.\textsuperscript{28} Compared to the corresponding Pd catalyst systems, the major advantages of Ni based catalyst are their much lower cost and increase reactivity toward readily available and inexpensive aryl chloride.\textsuperscript{29} The protocol for this amidation reaction utilizes Ni (0) in the form of Ni (PPh\textsubscript{3})\textsubscript{4} as a catalyst although it is air sensitive hence the use of inert atmosphere during preactivation.
1.2 STATEMENT OF PROBLEM

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 are few report of nickel catalyzed tandem reactions for the formation of C-N moiety compounds. It is the interest in this direction that prompted the present synthesis of benzenesulphonamide derivatives preferentially based on cheap Ni (II) precursor, suitable ligand and a mild reducing agent using the Buchwald-Hartwig protocol as shown in the structure below:
1.3 OBJECTIVE OF THE STUDY

i. To synthesize benzene sulphonamide and to use an efficient catalyst system for the amidation of aryl halides, preferentially based on a cheap Ni (II) precursor and a mild reducing agent.

ii. To characterize these synthesized products for structure elucidation using various spectroscopic technique like FT-IR, \(^1\text{H}\) and \(^{13}\text{C}\) –NMR.

iii. To evaluate these synthesized products for their biological activities

1.4 JUSTIFICATION OF THE STUDY

The upsurge of widespread multi-drug resistance microorganisms and emergence of new diseases have been reported as a major threat to human health. Thus there is a continue need for the synthesis of new organic compound as potential antimicrobial agent\(^{30}\).

The growing problem of antibiotic resistance has prompted renewed interest in sulfa drugs as a possible source of new therapeutic targets. This is because most disease causing microorganism needs DHPS to help make the molecule folate, which is required for the production of DNA and some amino acids. Hence, there is the need to develop a series of functionalized sulphanilamide with different substituents for structural-activity reaction purposes to avert the emergences of resistance, alter spectrum of activity, improve potency and ideally shorten the duration of therapy\(^{31}\).
2.0 LITERATURE REVIEW

Due to the broad applicability of sulphonamides, it is desirable to find general and effective methods for their synthesis. The following section provides several of the most common and recent methods of sulphonamide synthesis. The development of efficient methods for the synthesis of amides remains good tools because of their importance in chemistry and biology, with a wide range of industrial and pharmaceutical applications and as valuable intermediates in organic synthesis\textsuperscript{32}.

2.1 SULPHONAMIDES FROM SULFONYL CHLORIDES AND SULFONIC ACIDS

Ajani\textsuperscript{33} and coworkers synthesized a series of new N,N-diethylamide bearing sulphonamides (31a-e) via amidation of easily prepared benzene sulphonamide precursors (27a-e) and (28a-e). Benzenesulfonyl chloride 26 underwent condensation reaction with two different amino acids to afford \(N\)-disubstituted benzene sulphonamide (\(n=1\)) or with secondary amine (\(n=2, R\)) to give \(N, N\)-disubstituted benzene sulphonamide which on further treatment with oxalyl chloride 29 in the presence of one drop of DMF produces an acid chloride 30 which was converted to \(N,N\)-diethylsubstituted arylsulphonamide 31b by treating it with diethylamine in the presence of triethylamine base using dichloromethane as a solvent according to a known procedure\textsuperscript{34}.

\[
\text{SOCl}_2 + \text{HO-CH(CH}_3\text{)}_2 \text{N}_n \rightarrow \text{Na}_2\text{CO}_3/\text{H}_2\text{O} \text{S}_\text{N}_\text{Cl} \rightarrow \text{Stir at rt, 4h} \text{2M HCl, pH 2} \rightarrow \text{COOH}
\]

(a):\(n=1\)
(b):\(n=2\)
(c):\(R=H\)
(d):\(R=\text{CH}_3\)
(e):\(R=\text{CH(CH}_3)_2\)
The antimicrobial activity of these compounds along with streptomycin was investigated on *Escherichia coli* and *Staphylococcus aureus*. The results showed that this skeletal framework exhibited marked potency as antibacterial agents. The most active antibacterial agent against both targeted organisms was 31b.

Novel primary sulphonamide bearing 2,5-disubstituted-1,3,4-oxadiazole moiety 35 have successfully been prepared by Iqbal\(^3\) and coworkers through direct chlorosulfonation of phenyl substituent present on the second position of 5-mercapto-1,3,4-oxadiazole 33 using chlorosulfonic acid under anhydrous conditions. A common theme for these 35 derivatives is the requirement for a free mercaptoaryl group for an enhanced antiviral and antibacterial activity\(^\text{36}\).
Rehman and co-worker reported the reaction of benzenesulfonyl chloride 36 with 2-methoxyaniline 37 yielded \( N-(2\text{-methoxyphenyl})\)benzenesulfonamide 38, which on bromination with bromine in the presence of acetic acid gave \( N-(4,5\text{-dibromo-2-methoxyphenyl})\)benzenesulfonamide 39. The two products 38 and 39 on further treatment with alkyl halides/acyl halide in the presence of sodium hydride yielded N-substituted sulphonamide 40 and 41.
Argyropoulou and coworkers synthesized several thiazoles and benzothiazoles that carries a benzene sulphonamide moiety at position 2 of the heterocyclic nucleus by heating the appropriate heteroarylamine (benzo[d]thiazol-2-amine) 42 with the selected benzenesulphonyl chlorides 43 in pyridine for several hours to furnish Substituted N-(benzo[d]thiazol-2-yl)benzenesulphonamides 44. Nucleophilic addition of the NH2 group to the sulphonyl function of the benzenesulphonyl chlorides takes place at 60°C. All the sulphonamides and some of the nitro substituted derivatives had effective antibacterial properties against gram positive bacteria (MIC 0.3-100 µg/mg) such as Bacillus staphylococci and Streptococci including methicillin-resistant Staphylococcus Aureus.

R=H, 4-CH3, 6-F, 6-Cl, 6-OC2H5
R1= NHCOCH3, NO2, Cl

Scheme VIII Synthesis of substituted N-(benzo[d]thiazol-2-yl)benzenesulphonamides

Barrett and coworkers reported the use of Grignard reagent to increase diversity on sulfur in a one-pot sulphonamide synthesis. Aromatic halides are mixed with magnesium to form Grignard reagent 45, which can then attack sulfur dioxide to form sulfinic acid salt 46. Subsequent chlorination using sulfuryl chloride generates sulfonyl chloride, and aminolysis furnishes 47 in one-pot. A wide range of organohalides were studied, but only aromatic and heteroaromatic halides produced desirable results.
2.1.1 SULPHONAMIDES FROM SULPHENAMIDES

Another innovative example of sulphonamides synthesis is illustrated in the synthesis of 6-ethoxybenzothiazole-2-sulphonamide 49 (an antagonist of orotic acid) by Greenbaum$^{40}$. In this approach the 49 is reasonably effectively oxidized from 6-ethoxybenzothiazole-2-sulphenamide 48 using KMnO$_4$ with 64% yield.

![Scheme IX](image)

**Scheme IX** Sulphonamide formation via Grignard reagent

Revankar$^{41}$ and coworkers reported that, during their synthesis of pyrimidine-4-sulfonamide derivative 51 as potential antitumor drug, oxidation of sulfenamide 50 using one equivalent of m-CPBA produced 48% of the corresponding sulfonamide 51, this could be increased to 58% using four equivalents of m-CPBA in ethanol.
Scheme XI m-CPBA oxidation of sulfenamide to sulphonamide

2.1.2 SULFONAMIDES FROM N-ARYLATION

Transition-metal catalyzed C-N bond formation has been studied extensively, where the most well-known, palladium catalyzed N-arylation is the Buchwald-Hartwig reaction\textsuperscript{42-44} however there are few reports of N-arylation on sulfonamides. The first example used cupric acetate and arylboronic acid \textsuperscript{52} to give N-aryl sulfonamide \textsuperscript{53}. Lam\textsuperscript{45, 46} and coworkers described an effective protocol using 0.1 equivalent of copper (II) acetate in air, to give near-quantitative yield.

Scheme XII N-arylation of sulphonamide using Chan Lam reaction

More recently, Guo\textsuperscript{47} and coworkers have synthesized a range of sulfonamides using copper (I) catalyzed coupling using aryl bromide/iodide. During the optimization process, they found that using an amino acid as a ligand introduces several advantages such as easy removal after the reaction. After screening several amino acids, they found that N-
methylglycine and $N, N$-dimethylglycine are the most effective with Cu(I). Together with K$_3$PO$_4$ as base and DMF as the solvent, 54-55 can be generated in up to 99% yield.

\[
\text{Ar}-\text{X} + \text{R} - \text{SO}_2\text{N} - \text{R}^1 \xrightarrow{\text{Cu(I)}} \text{R} - \text{SO}_2\text{N} - \text{Ar}
\]

**Scheme XIII** Copper mediated N-arylation using amino acid as ligand

Cao$^{48}$ and coworkers reported the palladium catalyzed $N$-arylation of sulfonamides under microwave irradiation. In their report they describe the effect of modifying the ligands, bases and solvents, and identified optimal reaction conditions under microwave heating at 180 °C for 10 minutes. Unfortunately this method led to only modest yield of $N$-arylsulfonamides.

\[
\text{Cl} + \text{SO}_2\text{NH}_2 \xrightarrow{1\text{mol}\% \text{Pd(dba)}, 3\text{mol}\% \text{ligand}} \text{CsCO}_3(1.4\text{eq}) \xrightarrow{\text{Dioxane, Mw 180 °C}} \text{10min}} \text{SO}_2\text{N}\]

**Scheme XV** Palladium mediated N-arylation of sulphonamide under microwave
Rambabu and coworkers were able to synthesize 3-substituted benzothiazines 62 via AgNO\textsubscript{3} mediated O-(1-alkynl) benzenesulfonamide 61. The synthesis of the starting material 61 was carried out via Pd/C mediated coupling of O-iodobenzenesulfonamide 59 with terminal alkynes 60 in good yield\textsuperscript{50}.

![Scheme XVI](image)

**Scheme XVI** AgNO\textsubscript{3} mediated synthesis of 3-substituted benzothiazine

Silver nitrate facilitated the intra-molecular ring closure of 59 via a regioselective C-N bond forming reaction leading to the formation of 62 derivatives. All compound synthesized were evaluated for their cyclooxygenase (COX) inhibiting properties \textit{in vitro}. Some of which shown selectivity toward COX-2 over COX-1 inhibition.

### 2.1.3 SULFONAMIDES FROM SULFONATE ESTERS

Pentafluorophenyl (PFP) sulfonate esters 63 have been recently introduced to replace 64 for 20 preparations. The use of PFP sulfonate esters may introduce several advantages such as reduced toxicity, enhanced shelf stability, and makes them desirable as precursors. Caddick\textsuperscript{51} and coworker have reported that the aminolysis of sulfonates in refluxing THF can be used as an effective method for the synthesis of 64 in good to excellent yield. It was further shown that a range of amines (primary, secondary, aromatic, and aliphatic) could undergo reaction with 50 to produce a wide range of sulfonamides\textsuperscript{52}. 
Scheme XVII Ammonolysis of pentafluorophenyl sulfonate esters to generate sulphonamide

Caddick\textsuperscript{53} and coworkers have also reported aminolysis of 63 with various amines under microwave heating. All desired sulphonamides were generated in moderate to high yield while the reaction times were significantly reduced (5 min).

\begin{figure} [h]
\centering
\includegraphics[width=\textwidth]{schematic.png}
\caption{Scheme XVIII Yield reported from aminolysis under microwave irradiation}
\end{figure}

So far, all the above examples are focused on intermolecular aminolysis; however an intramolecular aminolysis was also reported by Caddick\textsuperscript{54} and coworkers in the formation of β-sultams 64 (cyclic sulfonamides), which are potential serine lactamase inhibitors in bacterial developed resistance to penicillin. Caddick \textit{et al.}\textsuperscript{54} reported the use of Mo(CO)\textsubscript{6} to catalyse N-O bond cleavage in isoxazolidine PFP sulfonate esters this was then followed by direct displacement of PFP by the intramolecular amine to give pure \textit{cis} β-sultams 65 27-58%

\begin{figure} [h]
\centering
\includegraphics[width=\textwidth]{schematic.png}
\caption{Scheme XIX Formation of β-sultams via N-O bond cleavage using Mo (CO)\textsubscript{6}}
\end{figure}
2.1.4 SYNTHESIS OF SCHIFF BASES OF SULPHONAMIDE

Schiff base is a nitrogen analogue of an aldehyde or ketone in which C=O group is substituted by a C=N-R group. It is also known as azomethine. Schiff bases are widely used for synthetic purpose by chemists\textsuperscript{55}. The synthesis of Schiff bases of sulphonamide by reaction of equimole of 3-methoxybenzene 66 and 3,4,5-trimethoxybenzene 67 dissolved in minimum amount of ethanol, followed by addition of 2ml of glacial acetic acid and reflux for 5-6 hrs to give 4-[(E)-(3-methoxyphenyl)methylidene]aminobenzenesulfonamide 68 was carried out by Kumar\textsuperscript{56} and coworkers.

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{H}_2\text{N} \\
\text{O} \\
\text{S} \\
\text{O} \\
\text{O} \\
\text{NH}_2 \\
\text{C}_2\text{H}_5\text{OH} \\
\text{glacial acetic acid, reflux for 6-5hrs} \\
\end{array}
\]

Scheme XX Synthesis of Schiff bases of Sulfonamide

2.1.5 MICROWAVE-ASSISTED SYNTHESIS FOR SULPHONAMIDE

An easy and handy synthesis of sulphonamides directly from sulphonic acids or its sodium salts is performed under microwave irradiation. This approach was reported to show a good functional group tolerance and the products were formed in excellent yield\textsuperscript{57}.
2.1.6 WATER-MEDIATED CATALYST PREACTIVATION: AN EFFICIENT PROTOCOL FOR C-N CROSS-COUPLING REACTION

Fors\textsuperscript{58} and coworkers successfully used a new biarylphosphine ligand (t-BuBrettphos) \textsuperscript{72} for palladium catalyzed cross coupling reactions of 1-chloro-2-methylbenzene \textsuperscript{69} and acetamide \textsuperscript{70} to produce N-phenylacetamide \textsuperscript{71} 83\%. It was reported that this system shows the highest turnover to date for these reactions, especially for aryl chloride substrates bearing an ortho substituent.

\[
\begin{align*}
\text{PhCl} + \text{CH\textsubscript{2}=N\textsubscript{2}} & \xrightarrow{1 \text{ mol}\% \text{ Pd}} \text{Ph} - \text{NH} - \text{C(O)} - \text{Ph} \\
\text{Cl} & \quad \text{NH}_2
\end{align*}
\]

\textbf{Scheme XXI} Water mediated efficient protocol for C-N cross-coupling

2.1.7 SULFONAMIDES AS THERAPEUTIC AGENTS

2.1.7.1 SYNTHESIS OF SULPHONMIDE AS HYPOGLYCEMIC AGENT

Weber\textsuperscript{59} and coworkers synthesized a second generation synthetic hypoglycemic agent (glyburide) which has a more complex structure in the sulfonylamide region of the molecule into which an additional pharmacophore group is added. It was synthesized from 2-methoxy-5-chlorobenzoic acid chloride \textsuperscript{73}, which is transformed 2-(benzylamino)-1-(5-chloro-2-methoxyphenyl)ethanone \textsuperscript{75} by reacting it with 2-phenylethylamine \textsuperscript{74}. This undergoes subsequent sulfonyl chlorination by chlorosulfonic acid, and then amination by ammonia, which gives 4-[2-(5-chloro-2-methoxyphenyl)-2-oxoethyl]aminomethyl]benzenesulfonamide \textsuperscript{76}. The resulting \textsuperscript{76} is reacted with cyclohexylisocyanate \textsuperscript{77} to give the desired 1-[4-[2-(5-chloro-2-methoxybenzamido)ethyl]-phenylsulfonyl]-3-cyclohexylurea \textsuperscript{78}. 

Scheme XXII Synthesis of Glyburide

This drug belongs to the second-generation sulfonylurea derivatives. Like all of the other oral hypoglycemic drugs examined, it is a β-cell stimulant in pancreas; but on the other hand, it increases the sensitivity to insulin, the degree to which it binds with target cells. At the same time, it differs in that it is easier to tolerate. The hypoglycemic effect sets in at significantly lower doses than with first-generation drugs. It is used for type II diabetes mellitus of medial severity with no expressed microvascular complications.

2.1.7.2 SYNTHESIS OF SULPHONAMIDE AS CARBONIC ANHYDRASE INHIBITOR

Roblin and coworkers synthesized acetazolamide by the reaction of ammonium thiocyanate 79 and hydrazine 80, forming hydrazino-N,N-bis-(thiourea) 81, which cyclised into 5-amino-1,3,4-thiadiazole-2-thiol 82 upon reaction with phosgene.
Acetylation of 82 with acetic anhydride gives 2-acetylamino-5-mercapto-1, 3,4-thiadiazol 83. The obtained product is chlorinated to give 2-acetylamino-5-mercapto-1,3,4-thiadiazol-5-sulfonyl chloride 84, which is transformed into N-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)acetamide 85 upon reaction with ammonia.

Scheme XXIII Synthesis of Acetazolamide

Acetazolamide is used for epilepsy in the absence of attacks and also in conjunction with other antiepileptic drugs. 80

2.1.7.3 SYNTHESIS OF SULPHONAMIDE AS ANTICANCER AGENT

Pazopanib hydrochloride is a potent and selective multi-targeted receptor tyrosine kinase with a sulphonamide moiety that blocks tumour growth and inhibits angiogenesis. The synthesis of pazopanib begins with methylation of 3-methyl-6-nitroindazole 86 with trimethyl orthoformate 87 in the presence of BF3-OEt to give 2,3-dimethyl-6-nitro-2H-indazole-ethane(1:1) 88 in 65% yield. Reduction of the nitro group was achieved via transfer hydrogenation to give 2, 3-dimethyl-2H-indazol-6-amine-ethane(1:1) 89 in 97% yield, and this was followed by coupling the aniline with 2,4-dichloropyrimidine 90 in a THF-ethanol mixture at elevated temperature to provide N-(2-chloropyrimidin-4-yl)-2, 3-dimethyl-2H-indazol-6-amine-ethane(1:1) 91 in 90% yield. The aniline nitrogen was then methylated using methyl iodide to give N-(2-chloropyrimidin-4-yl)-N, 2, 3-trimethyl-2H-
indazol-6-amine-ethane(1:1) \(92\) in 83% yield prior to coupling with 5-amino-2-methylbenzenesulfonamide \(93\) and salt formation using an alcoholic solution of HCl to furnish pazopanib hydrochloride \(94\) in 81% yield\(^6^2\).

\[
\begin{align*}
\text{Scheme XXIV Synthesis of Pazopanib Hydrochloride}
\end{align*}
\]

2.1.7.4 SYNTHESIS OF SULPHONAMIDE AS ANTIVIRAL AND HIV INHIBITOR

Recently, sulfa drugs were introduced as protease inhibitor thus, can be used as antiviral agent\(^6^3\). HIV protease is a proteolytic enzyme responsible for cleaving the large polyprotein precursor into biologically active protein product and this normally enhances the viral load in the host\(^6^4\). An inhibitor of this viral cleavage tend to reduce viral load hence manage infectivity. Amprenavir, a sulfa drug that acts as protease inhibitor is synthesized by heating benzyloxycarbonyl-epoxy \(95\) with 2-methylpropan-1-amine \(96\) in ethanol where the epoxide ring undergoes ring opening with amino group to form amino alcohol compound \(97\) which was then reacted with benzylchloroformate \(98\) in TEA and dichloromethane system for 6 hours to give \(99\). Reacting \(99\) with ethyl acetate \(100\) and anhydrous
hydrogen chloride gas at a lower temperature gave compound 101. Reacting 101 with N-succinimidyl-(s)-tetrahydrofuryl carbonate 102 in the presence of diisopropylethylamine and acetonitrile gave compound 103. Hydrogenation of 103 using Pd/C for 14 hours at room temperature produces compound 104. Its reaction with p-Nitrobenzenesulfonyl chloride 105 in the presence of a base gave compound 106. Reduction of 106 using Pd/C gave the final product [(1S, 2R)-3-[(4-aminophenyl) sulfonyl] (2-methylpropylamino)-2-hydroxy-1-(phenylmethyl] carbamic acid (3S)-tetrahydro-3-furanyl ester known as Amprenavir.
Scheme XXV Synthesis of Amprenavir

2.1.8 SYNTHETIC APPLICATIONS OF SULPHONAMIDE
Sulphonamides have been used in the field of synthetic organic chemistry. Some of these methods are discussed below.

2.1.8.1 SYNTHESIS OF SECONDARY AMINES FROM SULPHONAMIDES
Kan and Fukiyame reported an efficient synthetic method for the preparation of secondary amines using sulfonamides. In this method, primary amine $\text{107}$ was reacted with nitrobenzenesulfonyl chloride $\text{108}$ to give the corresponding sulfonamide $\text{109}$, which on alkylation with appropriate alkyl halide, followed by deprotection gave the secondary amine $\text{111}$. 

$$
\begin{align*}
\text{R-NH}_2 + \text{Cl-SO}_2\text{NO}_2 & \rightarrow \text{R-NH}_2 + \text{SO}_2\text{NO}_2 \rightarrow \text{R-NH}_2 + \text{SO}_2\text{NO}_2 \\
\text{Base} & \rightarrow \text{R-NH}_2 + \text{SO}_2\text{NO}_2 & \text{K}_2\text{CO}_3 & \rightarrow \text{R implant X}
\end{align*}
$$
2.1.8.2 SYNTHESIS OF SULFONAMIDE CHIRAL LIGANDS

Balsells and coworkers prepared new class of sulfonamide chiral ligands. These ligands are prepared from trans 1, 2- diaminocyclohexane by reaction with sulfonil chlorides to give aminosulfonamide compounds. These compounds are condensed with salicylaldehyde derivatives to provide a sulfonamide Schiff bases compound which represents a new class of chiral ligands.

Scheme XXVI Synthesis of sulphonamide-schiff base ligands
CHAPTER THREE

3.0 EXPERIMENTAL

3.1 GENERAL

All reactions including the pre-activation of the nickel(II) salt were carried out under an atmosphere of nitrogen. Also, the reagents were of technical grade. Nickel (II) chloride hexahydrate, triphenylphospine, benzenesulphonyl chloride, 2-chlorophenothiazine, 2-chloro-5-nitropyridine, 4-chloro-2,6-diaminopyrimidine and the solvent tert-butanol were all purchase from sigma-Aldrich while 2-bromoaniline and 2-chlorophenol were of BDH laboratory supplies. Column chromatography was carry out using Merck silica gel adsorbent 230-400 mesh using hexane-diethylether mixture as eluent in the ratio of 4:1. Melting points were determined with Fischer John’s melting point apparatus and are uncorrected. IR spectra were recorded on 8,400 Fourier Tranform Infrared (FTIR) spectrophotometer and are reported in wavenumber (cm$^{-1}$). IR analysis was done at National Research Institute for Chemical Technology (NARICT), Zaria, Kaduna state. Nuclear Magnetic Resonance ($^1$H-NMR and $^{13}$C-NMR) were determined using Jeol 400 MHz at Strathclyde University Scotland. Chemical shifts were reported in (δ) scale.

3.2 BENZENESULPHONAMIDE

Using a 100 ml Erlenmeyer flask, (2.1 g, 60 mmol) of ammonium hydroxide was added to (5.31 g, 30 mmol) of benzenesulfonyl chloride and stirred for five minutes, as product forms, the mixture warms up and thicken to a paste that was difficult to stir. 10 ml of distilled water was added and stirring continue for three minute, afterward the product was immersed on a water bath for about two minutes at 60-70°C. It was allowed to cool, and then chilled in ice-water. The solid product was collected in a Buchner funnel using suction filtration.
It was air dry and recrystallized from a 1:1 mixture of water and ethanol to give a glistening white solid benzenesulphonamide (1.1 g, 78%) with a melting point of 148-149°C (dec).

$^1$H-NMR (DMSO) $\delta$3.5 (s, 2H, NH), $\delta$7.37 (s, 1H, ArH), $\delta$7.58 (m, 2H, ArH), $\delta$ 7.58 (m, 2H, ArH)

3.3 GENERAL PROCEDURE FOR THE SYNTHESIS OF BIS(TRIPHENYLPHOSPHINE)NICKEL(II)CHLORIDE

This complex compound was prepared according to the procedure developed by Venanzi^{68}. A salt of nickel(II)chloride hexahydrate (2.38 g, 0.01 mole) dissolved in 2 ml of water and diluted with 50 ml glacial acetic acid and triphenylphosphine (5.25 g, 0.02 mole) ligand was dissolved in 25 ml of glacial acetic acid was added. The olive green microcrystalline precipitate obtained was kept in the solution of 99.5% glacial acetic acid for 24 hrs. It gave dark blue crystals of bis(triphenylphosphine)nickel(II)chloride which was filters off in a Buchner funnel, washed with glacial acetic acid and dried in a vacuum desiccator.

3.4 GENERAL PROCEDURE FOR THE SYNTHESIS OF VARIOUS SULPHONAMIDE DERIVATIVES

Nitrogen gas was introduced into a 50 ml two necked round-bottomed flask which was equipped with a magnetic stir bar under nitrogen inert atmosphere. Bis(triphenylphosphine)nickel(II)chloride (6.54 g, 0.01mol) and triphenylphosphine (5.25 g, 0.03 mol) was both added (ratio 1:3) and then the solvent (tertiary butanol 4 ml and distilled water 2 ml) (ratio of 2:1) was introduce through a syringe and stirred for 10 min. Afterward, it was heated at 80°C for 1.5 min. The catalyst preactivation was done totally under inert nitrogen atmosphere except during the heating at 80°C for 1.5 min. Thereafter, benzenesulphonamide (1.41 g, 0.01 mol), $K_2CO_3$ (1.38 g, 0.01 mol) and substituted heteroaryl- and aryl-halides were added to the mixture with the solvent tert-
butanol and water in the ratio of 2:1 under inert atmosphere. The entire mixture was refluxed with stirring for one hour at temperature of 100-110°C. The entire mixture was then cooled at room temperature, diluted with ethyl acetate, washed with water and purified via column chromatography.

3.4.1 N-(4-HYDROXYPHENYL) BENZENESULPHONAMIDE
This compound weighed (1.78 g, 71%) as creamy white solid melting at 126-127°C (dec). IR (KBr) $\nu_{\text{max}}$ 3,347.57 cm$^{-1}$ (OH stret), 3,258.84 cm$^{-1}$ (sec N-H stret), 3,057.27 cm$^{-1}$ (aromatic C-H stret), 1,568.18 cm$^{-1}$ (aromatic C=C stret), 1,325.14 cm$^{-1}$ (C-N stret), 1,164 (SO$_2$ stret), 740.69 cm$^{-1}$ (C-S stret). $^1$H-NMR (DMSO), $\delta$ 3.4 (s, br, 1H, NH), $\delta$ 7.24 (m, 2H, ArH), $\delta$ 7.39-7.40 (m, 4H, ArH), $\delta$ 7.57 (q, J= 5.69Hz, 2H), $\delta$ 7.85 (m, 1H, ArH). $^{13}$C-NMR $\delta$145-132 (aromatic carbons), $\delta$126-129 (C=C)

3.4.2 N-(2, 6H-DIAMINOPYRIMIDIN-4-YL) BENZENESULPHONAMIDE
This compound weighed (1.98 g, 75%) as a crystal white solid melting at 123-124°C (dec). IR (KBr) $\nu_{\text{max}}$ 3,401.58 cm$^{-1}$ (sec N-H stret), 1,569.14 cm$^{-1}$ (aromatic C=C stret), 1,303 cm$^{-1}$ (C-N stret), 1,150.58 cm$^{-1}$ (SO$_2$ stret). $^1$H-NMR (DMSO) $\delta$3.4 (s, 1H, NH), $\delta$5.7 (s, 1H, ArH), $\delta$6.33 (s, 2H, NH), $\delta$6.59 (s, 2H, NH), $\delta$7.32 (m, 1H, ArH), $\delta$7.58 (m, 2H, ArH), $\delta$7.83 (m, 2H, ArH).

3.4.3 N-(10H-PHENOTHIAZIN-1-YL) BENZENESULPHONAMIDE
This compound weighed (2.15 g, 92%) as a grey solid melting at 187-188°C (dec). IR (KBr) $\nu_{\text{max}}$ 3,336.96 cm$^{-1}$ (sec N-H stret), 3,069.81 cm$^{-1}$ (aromatic C-H stret), 1,576.86 cm$^{-1}$ (aromatic C=C stret), 1,310.67 cm$^{-1}$ (C-N stret), 1,145.75 cm$^{-1}$ (SO$_2$ stret), 726.22 cm$^{-1}$ (C-S stret). $^1$H-NMR (DMSO) $\delta$3.5 (s, 1H, NH), $\delta$6.66 (dd, J$_1$= 0.98Hz, J$_2$= 7.92Hz, 1H, ArH), $\delta$6.70 (d, J= 2.16Hz, 1H), $\delta$6.78 (m, 4H, ArH), $\delta$6.92 (d, J= 8.08Hz, 2H, ArH), $\delta$7.01 (td, J$_1$= 1.35Hz, J$_2$= 7.72Hz, 3H, ArH), $\delta$8.76 (s, 1H, ArH). $^{13}$C-NMR $\delta$144-122 (aromatic carbons), $\delta$117-115 (aromatic C=C).
3.4.4 N-(4-AMINOPHENYL) BENZENESULPHONAMIDE
This compound weighed (1.14 g, 46%) as a dull white solid melting at 142-143°C (dec).
IR (KBr) $\nu_{\text{max}}$ 3,341.78 cm$^{-1}$ (aromatic pri N-H stre), 3,261.74 cm$^{-1}$ (sec N-H stre),
3,071.74 cm$^{-1}$ (aromatic C-H stre), 1,568.18 cm$^{-1}$ (aromatic C=C stre), 1325.14 cm$^{-1}$ (C-
N stre), 1,157 cm$^{-1}$ (SO$_2$ stre), 706.93 cm$^{-1}$ (C-S stre). $^1$H-NMR (DMSO) $\delta$3.5 (s, 3H,
NH), $\delta$7.24 (m, 2H, ArH), $\delta$7.39 (m, 2H, ArH), $\delta$7.58 (m, 4H, ArH), $\delta$7.84 (m, 1H, ArH).

3.4.5 N-(4-NITROPYRIDIN-2-YL) BENZENESULPHONAMIDE
This compound weighed (2.22 g, 79%) as a light brown solid melting at 120-121°C (dec).
IR (KBr) $\nu_{\text{max}}$ 3,332.14 cm$^{-1}$ (sec amide N-H stre), 3,078.49 cm$^{-1}$ (Ar-CH stre), 1,567.21
cm$^{-1}$ (Ar C=C stre) 1,452.45 cm$^{-1}$ (N=O stre), 1,324.18 cm$^{-1}$ (C-N stre), 1,150.58 cm$^{-1}$
(SO$_2$ stre), 723.33 cm$^{-1}$ (C-S stre). $^1$H-NMR (DMSO) $\delta$7.24 (m, 1H, ArH), $\delta$7.39 (m,
2H, ArH), $\delta$7.84 (m, 1H, ArH), $\delta$8.63 (dd, $J_1=2.86$Hz, $J_2=8.74$Hz, 1H, ArH), $\delta$9.24 (d, $J=2.86$Hz, 1H, ArH).

3.5 ANTI-MICROBIAL ACTIVITY

The antimicrobial general sensitivity testing and minimum inhibitory concentration of all
the synthesized benzene sulphonamide derivatives alongside with that of tetracycline and
ketoconazole clinical standard were assayed on the test organism listed below using Agar
dilution technique$^{69}$.

**Bacteria**

*Staphylococcus aureus*  
Gram positive

*Enterococcus faecalis*  
Gram positive

*Salmonella typhi*  
Gram negative

*Klebsiella pneumonia*  
Gram negative

*Escherichia coli*  
Gram negative

*Pseudomonas aeruginosa*  
Gram negative
**Fungi**

*Candida albican*

*Aspergillus nigger*

In agar dilution test, micro-organisms are tested for their ability to produce visible growth on a series of agar plates with different concentration of synthesized derivatives. The lowest concentration of the synthesized benzene sulphonamide derivatives that will inhibit visible growth of micro-organism is the minimum inhibitory concentration (MIC).

**METHOD**-Agar dilution technique was employed by weighing a specified amount (20 mg) of synthesized benzene sulphonamide derivatives dissolved in DMSO and then mixing with prepared Mueller Hinton agar medium on a plate to give a known value (concentration) after which it was allowed to dry for about 30 min at 50°C using a dryer before streaking the organism suspension on the surface of the dried Mueller Hinton agar plate using a standardized inoculum of Mcfarlan 0.5.

**MATERIALS**

19 ml sterile molten agar (Mueller Hinton agar)
Sterile petri dish
Sterile test tube
Test organism suspension 0.5 Mcfarland
Inoculating loop
DMSO
Sterile 1 ml, 2 ml and 10 ml pipettes

**PROCEDURE**: Preparation of stock solution of the synthesized product was carryout by weighing out 20 mg of each and dissolving them in 5 ml of DMSO, that gave 4 mg/ml. Using two-fold serial dilution technique the following concentrations were obtained for each of the derivatives and the standard(tetracycline and ketoconazole): 2000 µg/ml, 1000 µg/ml, 500 µg/ml, 250 µg/ml, 125 µg/ml, 62.50 µg/ml, 31.25 µg/ml and 15.63 µg/ml. 1ml of each stock concentration was transferred into each plate covered with 19ml of molten agar to arrive at the final concentration require for the test.
The plates were allowed to set after which the surface was dried by exposing the surface to the heat in the dryer at 45°C for 30 min and then, allowed to cool before streaking the microbial suspension on them and incubated at 37°C for bacterial suspension and 28°C for fungal for 24 and 48 h respectively.
CHAPTER 4

4.0 RESULTS AND DISCUSSION

4.1 BENZENESULPHONAMIDE

On stirring ammonium hydroxide with benzenesulfonyl chloride for five min, benzenesulphonamide was obtained as a shiny white solid with a melting point of 148-149°C (dec).

\[ \text{SOCl}_2 + \text{NH}_3 \xrightarrow{\text{stir for 5 minute}} \text{SO-O-NH}_2 + \text{HCl} \]

The proposed mechanism of this reaction is as shown in the scheme below

\[ \text{SOCl}_2 + \text{NH}_3 \rightarrow \text{SO-O-NH}_2 + \text{HCl} \]

**Scheme XXVI** Mechanism of reaction for the formation of benzenesulphonamide

The assigned structure is supported by spectral analysis. The absorption band at \( \delta 3.5 \) (s, 2H) is due to N-H, \( \delta 7.37 \) (s, 1H) is due to C\(_4\) proton and \( \delta 7.58 \) (m, 2H) is due to C\(_3\) and C\(_5\) while \( \delta 7.85 \) (m, 2H) is due to C\(_2\) and C\(_6\) protons.
4.2 N-(4-HYDROXYPHENYL) BENZENESULFONAMIDE

The water promoted activation of bis (triphenylphosphone)nickel(II)chloride is as shown below

$$\text{NiCl}_2(\text{PPh}_3)_2 + 2\text{PPh}_3 + \text{H}_2\text{O} \rightarrow (\text{PPh}_3)_2\text{Ni}(0) + \text{O=PPh}_3 + 2\text{HCl}$$

A mixture of bis(triphenylphosphine)nickel(II)chloride and triphenylphosphine in a solvent of tertiary butanol and water was preactivated in a 100 ml two neck flask for 2 minutes at 80°C, while monitoring it, the dark green colour of the mixture changed as the two component of the mixture eventually dissolved to form a pale greenish solution after which benzenesulphonamide 20, 4-chlorophenol 113 and potassium carbonate with a further addition of tertiary butanol and water in a ratio of 2:1 was added. On stirring for about 1 hour at 110°C, N-(4-hydroxyphenyl)benzenesulphonamide 21 was obtained as a milky white solid with a melting point of 126-127°C (dec).

The assigned structure is supported by spectral analysis. The infrared spectrum showed bands at 3,347.57 cm\(^{-1}\) due to OH, 3,258.84 cm\(^{-1}\) due to secondary N-H, 3,057.27 cm\(^{-1}\) due to aromatic C=H stretching, 1568 cm\(^{-1}\) due to aromatic C=C stretching. 1,325.14 cm\(^{-1}\) is due to C-N stretch while the band at 1,164.08 cm\(^{-1}\) is due S=O stretching and 740.69 cm\(^{-1}\) is due to C-S stretching. The absorption band at $\delta$3.40 (s, br, 1H) is due to N-H. $\delta$7.24 (m, 2H, ArH) is due to C8 and C12 protons, $\delta$7.40 (m, 4H) is due to C2, C3 , C5 and C6 protons while $\delta$7.57 (q, J= 5.69Hz, 2H) is due to C11 and C9 protons and $\delta$7.85 (m, 1H) is due to C10 proton. The $^{13}$C-NMR absorption bands at $\delta$145-132 is due to aromatic carbon while bands at $\delta$126-129 is due to C=C bonding.
4.3 N-(2, 6-DIAMINOPYRIMIDIN-4-YL) BENZENESULFONAMIDE

The water promoted activation of bis(triphenylphosphine)nickel(II)chloride is as shown below

\[ \text{NiCl}_2(\text{PPh}_3)_2 + 2\text{PPh}_3 + \text{H}_2\text{O} \rightarrow (\text{PPh}_3)_2\text{Ni(0)} + \text{O=PPh}_3 + 2\text{HCl} \]

A mixture of bis(triphenylphosphine)nickel(II)chloride and triphenylphosphine in a solvent of tertiary butanol and water was preactivated in a 100 ml two neck flask for 2 minutes at 80°C, while monitoring it, the dark green colour of the mixture changed as the two component of the mixture eventually dissolved to form a pale greenish solution after which benzenesulphonamide 20, 4-chloro-2,6-diaminopyrimidine 114 and potassium carbonate with a further addition of tertiary butanol and water in a ratio of 2:1 was added. On stirring for about 1 hour at 110°C, N-(4-hydroxyphenyl)benzene sulphonamide 22 was obtained as a milky white solid with a melting point of 123-124°C (dec).

![Chemical structure](image)

The assigned structure is supported by spectral analysis. The infrared spectrum show bands at 3401.58 cm\(^{-1}\) due to secondary N-H stretch, 1569.14 cm\(^{-1}\) due to aromatic C=C and 1303 cm\(^{-1}\) is due to C-N stretch while 1150.58 cm\(^{-1}\) is due to S=O stretching. The absorption band at \(\delta\)3.40 (s, 1H) is due to N-H, \(\delta\)5.70 (s, 1H) is due to C\(_5\) proton, \(\delta\)6.33 (s, 2H) is due to primary N-H, \(\delta\)6.59 (s, 2H) is due to primary N-H while \(\delta\) 7.32 (m, 1H) is due to C\(_{10}\) proton, \(\delta\)7.58 (m, 2H) is due to C\(_9\) and C\(_{11}\) protons, \(\delta\)7.83(m, 2H) is due to C\(_8\) and C\(_{12}\) proton.
4.4 N-(10H-PHENOTHIAZIN-1-YL) BENZENESULFONAMIDE

The water promoted activation of bis(triphenylphosphine)nickel(II)chloride is as shown below

\[
\text{NiCl}_2(\text{PPh}_3)_2 + 2\text{PPh}_3 + \text{H}_2\text{O} \rightarrow (\text{PPh}_3)_2\text{Ni}(0) + \text{O=PPh}_3 + 2\text{HCl}
\]

A mixture of bis(triphenylphosphine)nickel(II)chloride and triphenylphosphine in a solvent of tertiary butanol and water was preactivated in a 100 ml two neck flask for 2 minutes at 80°C, while monitoring it, the dark green colour of the mixture changed as the two component of the mixture eventually dissolved to form a pale greenish solution after which benzene sulphonamide 20, 2-Chlorophenothiazine 115 and potassium carbonate with a further addition of tertiary butanol and water in a ratio of 2:1 was added. On stirring for about 1 hour at 110°C, N-(4-hydroxyphenyl)benzene sulphonamide 23 was obtained as a milky white solid with a melting point of 187-188°C (dec).

The assigned structure is supported by spectral analysis. The infrared spectrum show bands at 3,336.96 cm\(^{-1}\) due to secondary N-H stretch, 3,069.81 cm\(^{-1}\) due to aromatic C-H, 1576.86 cm\(^{-1}\) due to aromatic C=C, 1310.67 cm\(^{-1}\) due to C-N stretching while 1,145.75 cm\(^{-1}\) is due to S=O stretching and 726.22 cm\(^{-1}\) is due to C-S stretching. The absorption band at \(\delta\)3.40 (s, 1H) is due to N-H, \(\delta\)6.66 (dd, \(J_1= 0.98\text{Hz}, J_2= 7.92\text{Hz}, 2\text{H}\)) is due to C\(_2\) and C\(_4\) protons, \(\delta\)6.70 (d, \(J= 2.16\text{Hz}, 1\text{H}\)) is due to C\(_3\) proton, \(\delta\)6.78 (m, 4H) is due to C\(_6\)-C\(_9\) protons, \(\delta\)6.92 (d, \(J= 8.08\text{Hz}, 2\text{H}\)) is due to C\(_{16}\) and C\(_{17}\) protons, \(\delta\)7.01 (td, \(J_1= 1.35\text{Hz}, J_2= 7.72\text{Hz}, 3\text{H}\)) is due to C\(_{16}\), C\(_{18}\) and C\(_{19}\) protons and \(\delta\)8.76 (s, 1H) is due to N\(_{10}\) proton.\(^1\)C-NMR \(\delta\)144-122 is due to aromatic carbons while \(\delta\)117-115 is due to aromatic C=C.
4.5 N-(4-AMINOPHENYL) BENZENESULFONAMIDE

The water promoted activation of bis(triphenylphosphine)nickel(II)chloride is as shown below

\[ \text{NiCl}_2(\text{PPh}_3)_2 + 2\text{PPh}_3 + \text{H}_2\text{O} \rightarrow (\text{Ph}_3\text{P})_2\text{Ni}(\text{O}) + \text{O=PPh}_3 + 2\text{HCl} \]

A mixture of bis(triphenylphosphine)nickel(II)chloride and triphenylphosphate in a solvent of tertiary butanol and water was preactivated in a 100 ml two neck flask for 2 minutes at 80°C, while monitoring it, the dark green colour of the mixture changed as the two component of the mixture eventually dissolved to form a pale greenish solution after which benzenesulphonamide 20, 2-bromoaniline 116 and potassium carbonate with a further addition of tertiary butanol and water in a ratio of 2:1 was added. On stirring for about 1 hour at 110°C, N-(4-hydroxyphenyl)benzene sulphonamide 24 was obtained as a milky white solid with a melting point of 142-143°C (dec).

The assigned structure is supported by spectral analysis. The infrared spectrum show bands at 3,341.78 cm\(^{-1}\) aromatic primary N-H stretch, 3,261.74 cm\(^{-1}\) secondary N-H, 3,071.74 cm\(^{-1}\) is due to aromatic C-H, 1568.18 cm\(^{-1}\) is due to aromatic C=C stretching, 1325.14 cm\(^{-1}\) is due to C-N, 1,157 is due to S=O stretching and 706 cm\(^{-1}\) due to C-S stretching. The absorption band at \(\delta\) 3.40 (s, 3H) is due N-H, \(\delta\) 7.24 (m, 1H) is due to C\(_{10}\) proton, \(\delta\) 7.39(m, 2H) is due to C\(_9\) and C\(_{11}\) protons, \(\delta\) 7.58 (m, 4H) to C\(_2\), C\(_3\), C\(_5\) and C\(_6\) protons while \(\delta\) 7.84 (m, 2H) is due to C\(_8\) and C\(_{12}\) carbon protons.
4.6 N-(4-NITROPYRIDIN-2-YL) BENZENESULFONAMIDE

The water promoted activation of bis(triphenylphosphone)nickel(II)chloride is as shown below

\[
\text{NiCl}_2(\text{PPh}_3)_2 + 2\text{PPh}_3 + \text{H}_2\text{O} \rightarrow (\text{Ph}_3\text{P})_2\text{Ni(0)} + \text{O=PPh}_3 + 2\text{HCl}
\]

A mixture of bis(triphenylphosphine)nickel(II)chloride and triphenylphosphine in a solvent of tertiary butanol and water was preactivated in a 100 ml two neck flask for 2 minutes at 80°C, while monitoring it, the dark green colour of the mixture changed as the two component of the mixture eventually dissolved to form a pale greenish solution after which benzenesulphonamide 20, 2-chloro-5-nitropyridine 117 and potassium carbonate with a further addition of tertiary butanol and water in a ratio of 2:1 was added. On stirring for about 1 hour at 110°C, N-(4-hydroxyphenyl)benzene sulphonamide 25 was obtained as a milky white solid with a melting point of 120-121°C (dec).

The assigned structure is supported by spectral analysis. The infrared spectrum show bands at 3,332.14 cm\(^{-1}\) due to secondary N-H stretch, 3,078.49 cm\(^{-1}\) due to aromatic CH, 1567.21 cm\(^{-1}\) is due to aromatic C=C stretch, 1,452.45 cm\(^{-1}\) is due to N=O, 1,324.18 cm\(^{-1}\) is due to C-N while 1,150.58 cm\(^{-1}\) is due S=O and 723.33 cm\(^{-1}\) is due to C-S stretching. The absorption band at 3.50 (s, 1H) is due to N-H, 7.24 (m, 1H) is due to C\(_{10}\) proton, 7.39 (m, 2H) is due to C\(_9\) and C\(_{11}\) protons, 7.58 (m, 2H) is due to C\(_8\) and C\(_{12}\) protons, 7.84 (m, 1H) is due to C\(_6\) proton, 8.63 (dd, J\(_1=\) 2.86Hz, J\(_2=\) 8.74Hz, 1H) is due to C\(_5\) proton while 9.34 (d, J= 2.86Hz, 1H) is due to C\(_3\) proton.
The mechanism for the preparation of compounds 21, 22, 23, 24 and 25 proceed through the following steps.

The first step in the catalytic cycle is the oxidative addition of Ni (0) to the hetero halide. In the second step, the Ni (II) –hetero amide can be formed by direct displacement of the halide by the amide via a Ni (II) alkoxide intermediate via amide binding to the highly active Nickel complex and deprotonation by the base. Finally, a reductive elimination result in the formation of the desired C-N bond and the Ni (0) catalyst is regenerated.
4.7 ANTIMICROBIAL EVALUATION

All synthesized compounds were evaluated for their antibacterial and antifungal activities, the following compounds were found to be sensitive to the organism listed below:

<table>
<thead>
<tr>
<th>Compound Name</th>
<th>Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. N-(4-aminophenyl) benzenesulfonamide</td>
<td><em>Aspergillus niger</em></td>
</tr>
<tr>
<td>II. N-(4-nitropyridin-2-yl) benzenesulfonamide</td>
<td><em>Staphylococcus aureus, Klebsiella pneumonia, Enterococcus faecalis</em></td>
</tr>
<tr>
<td>III. N-(2,6-diaminopyrimidin-4-yl) Benzenesulfonamide</td>
<td><em>Candida albicans, Aspergillus niger</em></td>
</tr>
<tr>
<td>IV. N-(4-hydroxyphenyl) benzenesulfonamide</td>
<td><em>Staphylococcus aureus, Salmonella typhi, Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td>V. N-(10H-phenothiazin-1-yl) benzenesulfonamide</td>
<td><em>Staphylococcus aureus, Salmonella typhi</em></td>
</tr>
<tr>
<td>VI. benzenesulfonamide</td>
<td><em>Aspergillus niger</em></td>
</tr>
</tbody>
</table>

Table: Minimum Inhibitory Concentration of Synthesized Compound

<table>
<thead>
<tr>
<th>Antibacterial MIC (µg/ml) Test</th>
<th>S.aureus</th>
<th>K.pneumonia</th>
<th>S.typhi</th>
<th>P.aeruginosa</th>
<th>E.coli</th>
<th>E.faecalis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>II</td>
<td>500</td>
<td>100</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>100</td>
</tr>
<tr>
<td>III</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>IV</td>
<td>500</td>
<td>+</td>
<td>500</td>
<td>250</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>V</td>
<td>250</td>
<td>+</td>
<td>1000</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
The antimicrobial data reveals that compounds II, IV and V were found to be active against *S.aureus*. IV and V shows activity against *S.typhi*, II and III show activity against *P.aeruginosa* while II is active against *E.faecalis*. Compounds I, III and VI showed no activity against bacteria microorganism. Also, it was observe that all synthesized derivatives were inactive toward *E.coli*.

The antifungal result showed that compounds I, III and IV were active against *A.nigrier* while III was active against *C.albican*.

The comparative study of the effect of synthesized products and standard used (ketoconazole and tetracycline) revealed that some of the tested compounds showed significant activity but no improved potency was achieved when their respective MIC (µg/ml) were compared to the standard used as can be seen in the table above.
CHAPTER FIVE

5.0 CONCLUSION

The synthesis of benzene sulphonamide and its transformation to the various substituted benzene sulphonamide derivatives via Buchwald-Hartwig tandem amidation protocol has been achieve successfully. The assigned structures were supported by spectral analysis. Also, some of the synthesized product were biologically active but showed no improvement when compared to the standard that was used.
REFERENCES


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Figure 1 IR-spectral chart of N-(4-hydroxyphenyl) benzenesulphonamide
Figure 2 IR-spectral chart of \(N\)-(2,6-diaminopyrimidin-4-yl) benzenesulphonamide
Figure 3 IR-spectral chart of $N$-(10H-phenothiazin-1-yl) benzenesulphonamide
Figure 4 IR-spectral chart of N-(4-aminophenyl) benzenesulphonamide

Comment; 
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Date/Time;  3/14/2013 11:32:06 AM  
Resolution; 
Figure 5 IR-spectral chart of N-(4-nitropyridin-2-yl) benzenesulphonamide
Figure 6: H-NMR-spectral chart of benzenesulphonamide.
Figure 7: H-NMR spectral chart of N-(4-hydroxyphenyl)benzenesulphonamide.
Figure 8, H-NMR spectral chart of N-(2,6-diaminopyrimidin-4-yl)benzenesulphonamide.
Figure 9: NMR spectral chart of N-(10H-phenothiazin-1-yl) benzensulfonamide
Figure 10: H-NMR spectral chart of N-(4-aminophenyl) benzene sulfonamide.
Figure 11: H-NMR spectral chart of N-(4-nitropyridin-2-yl) benzene sulphonamide
Figure 12: 'H-NMR spectral chart of N-(4-hydroxyphenyl) benzene sulfonamide.
Figure 12: $^{13}$C-NMR spectral chart of N-(10H-phenothiazin-1-yl)benzenesulphonamide.