American Journal of IT and Applied Sciences Research
Vol. 1(4), pp. 1-11, September, 2022

ISSN: 2831-4840
https://www.mprijournals.com/

Full Length Research

Empirical Analysis of Synthesis and Antimicrobial Activities of 1-Methyl-4-Nitro-Imidazole-5-N, N-Diethylsulphonamide

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Accepted September, 10, 2022

Abstract: There is high level of antimicrobial resistance globally. Most commercial drugs are now becoming ineffective everyday. Hence there is a need to develop new antimicrobial drugs. The aim of the research was to synthesize 1-methyl-4-nitro-imidazole-5-N,N-diethylsulphonamide and determine its antimicrobial activities against bacteria and fungi. N,N′-Dimethyloxamide was synthesized from reaction between diethyl oxalate and methyl amine. The compound became cyclized on reacting with phosphorus (V) chloride to form 1-Methyl-5-chloroimidazole. 1-Methyl-5-chloroimidazole was subjected to nitration using nitric acid and sulphuric acid to give 1-Methyl, 4-nitro-5-chloroimidazole. The treatment of 1-Methyl, 4-nitro-5-chloroimidazole with hydrogen sulphide resulted in the formation of 1-Methyl, 4-nitro-5-thiolimidazole which was converted to 1-Methyl-4-nitro-imidazole-5-sulphonyl chloride. The compound was reacted with diethyl amine leading to the synthesis of 1-methyl-4 nitro-imidazole-5 –N,N-diethylsulphonamide. Antimicrobial activities of 1-methyl-4-nitro-imidazole-5-N, N-diethylsulphonamide was investigated using four bacteria and four plant pathogenic fungi. The results showed that the synthesized compound was active against tested organism, even though the standard used was more active.

Keywords: 1-methyl-4-Nitro-Imidazole-5-N: N-diethylsulphonamide: Antimicrobial: Pathogenic: Nitration: Imidazole: Aromatic Heterocycle

Cite this Article as: Owolabi, B. J., Adewole, E. A., Olunaike, J. H. **&** Oni, E. A. (2022). Empirical Analysis of Synthesis and Antimicrobial Activities of 1-Methyl-4-Nitro-Imidazole-5-N, N-Diethylsulphonamide. American Journal of IT and Applied Sciences Research, 1(4): 1-11.

1.0 Introduction of the Study

Imidazoles are an important heterocyclic structural motif in functional molecules and are utilized in a diverse range of applications. Despite recent advances, the development of novel methods for the region controlled synthesis of substituted imidazoles is of strategic importance. Kashyap et al. (2011) argued that this is due to the preponderance of applications to which this important heterocycle is being deployed, such as the traditional applications in pharmaceuticals and agrochemicals to emerging research into dyes for solar cells and other optical applications functional materials, and catalysis. It is due to their versatility and utility in a number of these areas that expedient methods for the synthesis of imidazoles are both highly topical and necessary (Kashyap et al., 2011; Valverde & Torroba, 2005; Shabalin, 2020). This review is focused on recent advances in the synthesis of imidazoles and is organized via the sorts of bond disconnections that were employed in order to construct the heterocycle. The bonds formed in the reaction are highlighted by being red colored throughout the review and the standard numbering of imidazoles is used in the description of disconnections (Amir, 2007; Singh & Kapoor, 2008).

Medicinal chemistry is the discipline concerned with determing the influence of chemical structure on biological activity and in the practice of medicinal chemistry developed from an empirical one involving organic synthesis of new compound based largely on the modification of structure and then identifies their biological activity (Abdel-Hafez et al., 2008). Medicinal chemistry concerns with the discovery, development, interpretation and the identification of mechanism of action of biologically active compounds at the molecular level. Various biologically active synthetic compounds have five-membered nitrogen-containing heterocyclic ring in their structures (Colussi & McMasters, 2004). Structural frameworks have been described as privileged structures and in particular, N-containing polycyclic structures have been reported to be associated with a wide range of biological activity. In the field of five membered heterocyclic structures imidazole nucleus shows various properties. The high therapeutic properties of the imidazole related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents (Valverde et al., 2005).

Imidazole drugs have broadened scope in remedying various dispositions in clinical medicines. Medicinal properties of imidazole include anticancer, b-lactamase inhibitors, 20- HETE (20-Hydroxy-5,8,11,14-eicosatetraenoic acid) synthase inhibitors, carboxypeptidase inhibitors, hemeoxygenase inhibitors, antiaging agents, anticoagulants, anti-inflammatory, antibacterial, antifungal, antiviral, antitubercular, antidiabetic and antimalarial (Dandale et al., 2012). This group presents in azoles antifungal which inhibit the accumulation of methylated sterols destroy the composition of the lipid bilayer of membranes. Some imidazole drugs, at high concentrations, could exert direct inhibitory action on membranes, without interference with sterols and sterol esters (Ukonu et al., 2022; Ubreye Benjamin et al., 2022; Ukonu et al., 2022; Owolabi et al., 2022). Infectious microbial disease causes worldwide problem, because microbes have resisted prophylaxis or therapy longer than any other form of life. In recent decades, problems of multidrug-resistant microorganisms have reached an alarming level in many countries around the world (Torroba et al., 2005). Resistance of anti-microbial agents such as β-lactam antibiotics, macrolides, quinolones and vancomycin etc. and different species of bacteria causes increased important global problem. Imidazole and its derivatives are reported to be physiologically and pharmacologically active and find applications in the treatment of several diseases (Kumar et al., 2010).

1.1 **Specific objectives of the Research**

The specific objectives are to:

(i) Synthesize 1-methyl-4-nitro-5-N, N-diethylsulphonamide

(ii) Investigate antimicrobial activities of the 1-methyl-4-nitro-5-N, N-diethylsulphonamide

2.0 Literature Review of the Study

2.1 Structure and pharmacological activities

Imidazoles are well known heterocyclic compounds which are common and have important feature of a variety of medicinal agents. Imidazole is a 5-membered planar ring, which is soluble in water and other polar solvents (Eshiett et al., 2022; Osho & Haruna, 2022;

Shumi et al., 2021; Chala et al., 2022; Enyi et al., 2022). It exists in two equivalent tautomeric forms because the hydrogen atom can be located on either of the two nitrogen atoms. It is a highly polar compound, as evidenced by a calculated dipole of 3.61D, and is entirely soluble in water. The compound is classified as aromatic due to the presence of a sextet of π-electrons, consisting of a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring. Imidazole is amphoteric, *i.e.* it can function as both an acid and as a base (Sperry, 2005; Jason, 2020). On the basis of various literature surveys Imidazole derivatives shows various pharmacological activities:Anti fungal and Anti-bacterial activity Anti inflammatory activity and analgesic activity Anti tubercular activity Anti depressant activity Anti cancer activity Anti viral activity Antileishmanial activity (Kapoor et al., 2008; Nagalakshmi, et al., 2008; Valverde & Torroba, 2005; Varma, 2008). Imidazole is a five-membered aromatic molecule containing two annular nitrogen atoms. One nitrogen behaves like a pyrrole-type nitrogen and the other one shows a close resemblance to a pyridine-type nitrogen (Pandeya, 2004; Liu, 2001; Reddy et al., 2004).The molecular formula of imidazole is C3H4N2and its molar mass is 68.08 g mol-1 (Kapoor, 2008) reported that it is a five-membered aromatic heterocycle where two nitrogen atoms substituting two CH- groups. The two nitrogen atoms are non-adjacent positions (Singh, 2008). Imidazole is a planar molecule; so there is an unshared electron pair under a nitrogen in a sp2 orbital. This electron pair is responsible by various of chemical properties of imidazole, such as the basicity of molecule. Free imidazole is not frequently found in nature. However, the imizadole derivatives are extended in nature, for examples: the amino acid histidine or the compounds histamine, bezimidazole and some alkaloids have the imidazole ring in their structures (Jain & Sharma, 2005; Lednicer & Mitscher, 1984).

2.2 Physical Properties

i) Imidazole is a white or colorless solid (ii) It can show a prismatic crystal appearance. (iii) Imidazole is highly soluble in water, ethanol, ethyl ether and chloroform. (iv) It is insoluble in non-polar solvents. (v) In water, it produces an alkaline solution. (vi) Its melting point is 88-9^{o}C and its boiling point is 256^{o}C. (vii) Imidazole has a molecular weight of 68.077g/mol with chemical formular $C_3H_4N_2$. (viii) Imidazole has a density of 1.23 g/cm^3 (Jain & Sharma, 2005). Imidazole exists as a resonance hybrid, the positions-4 and-5 are equivalent in the unsubstituted imidazole (Finar, 2006; Grimmett, 1997; Shabalin et al., 2020). Free imidazole is not frequently found in nature. However, the imizadole derivatives are extended in nature, for examples: the amino acid histidine or the compounds histamine, bezimidazole and some alkaloids have the imidazole ring in their structures (De Paula et al., 2010).

2.2 Chemical Properties

Imidazole is a 5-member rings that show two tautomeric structures due the positive charge can be located in both of the nitrogen atoms, thus the hydrogen binds to the nitrogen atom can be removed easily because the lesser electron density of this nitrogen atom (Eshiett et al., 2022; Osho & Haruna, 2022; Shumi et al., 2021). On the other hand, the other nitrogen atom has an unshared electron pair in a sp2 orbital that can accept protons. Consequently, imidazole shows an amphoteric behavior: it can act as a weak base or a weak acid (Solanki et al., 2012). Imidazole is used as raw material by the pharmaceutical industries for manufacturing anti-fungal drugs such as ketoconazole and clotrimazole or the bactericide imazilil and prochloraz. Similarly, the pesticide industries use the imidazole as intermediary in the synthesis of some pesticides and insecticides. It can also be used as corrosion inhibitor of metals such as copper. Moreover, imidazole has found application as epoxy curing agent, to improve the electrical properties in electronic devices (Chala et al., 2022; Enyi et al., 2022). Owing to the fact an imidazole ring is present in the amino acid histidine, imidazole solutions is extensively apply in molecular biologytechniques to purify recombinant proteins through metal affinity chromatography (IMAC). The proteins can be expressed with a histidine tails to promote the retention in a chromatography (Wright et al., 2005). The column that contains nickel ions and then, imidazole solution are used to displace the histidine tagged protein. Health effects/safety hazards: Imidazole is harmful by oral ingestion. It is also corrosive and can cause severe skin burns and eye damage (Kiran & Reddy, 2004).

3.0 Methodology of the Study

In this study, reagents such as diethyl oxalate, methylamine, phosphorus pentachloride, hydrochloric acid, sulphuric acid, dry ethanol, sodium carbonate, sulphuric acid, distilled water, chloroform, calcium chloride, nitric acid, sodium metal, iron sulphide, potassium

permanganate, diethylamine. Materials: Separating funnel, measuring cylinder, 250ml/500ml conical flask, filter paper, beaker, melting point apparatus, weighing balance, Buckner funnel, fume cupboard, thermometer, water bath, vacuum pump, reflux condenser, dropping pipette, clamp, magnetic stirrer, water bath, two neck flask, clamp, steel head, crucible.

3.1.1 Synthesis of 1-Methyl-5-Chloroimidazole

80.15g of $Pcl_5$was mixed with 26.72g of methyloxamide which gives Phosphorus-oxy- chloride.

3.1.2 Synthesis of Imidazole Compound: Sodium carbonate (100g) was mixed with distilled water to neutralize it. Sodium carbonate solution was added dropwise to Phosphorus-oxy-chloride, CO_2 is given off and this was exothermic reaction. The neutralization reaction was complete there is no more fuming. Heating Na_2CO_3 to the Phosphorus-oxy-chloride till it is basic and there is no more effervescence. A brownish coloured imidazole compound was obtained.

3.1.3 Separating Imidazole Compound: 200 ml of chloroform was added to the solution (brownish coloured imidazole compound) in the separating funnel, the chloroform and imidazole compound settled beneath while water was at the top, the chloroform and the solution was shaken together and a two distinct layer was formed. This was extracted 3-4 times, the imidazole and chloroform was separated out. $CaCl_2$ was dropped in the solution of imidazole and chloroform and left for 24hrs. ($CaCl_2$ serves as a drying agent) The solution of imidazole with chloroform undergoes distillation, chloroform was distilled off and a brownish colour of imidazole compound was obtained.

3.1.4. Synthesis of 1-Methyl-4-nitro-5-chloroImidazole: The compound can only be attacked at position 4,5 by nitrating at position 4. 20ml of conc. HNO_3 was added to 10ml of the brownish imidazole compound and this was evaporated to dryness using a water bath for 6hrs and this gives imidazole nitrate. The imidazole nitrate was heated with conc. $H_2SO_4$for 3hrs and a yellow crystals was obtained. 50ml of H_2SO_4 was measured using a measuring cylinder and was added to the 15g of yellow crystal and heat on water bath for 3hrs. Ice was added to the compound obtained and this was stirred together, buckner funnel coupled with vacuum pump was used for the filtration process. The filtrate was dried under the sun and a greenish yellow solid compound was obtained (5-chloro,1-methyl, 4-nitro- imidazole).

3.1.5. Synthesis of 1-methyl-4-nitro-5-thiolimidazole: The compound was poured inside the beaker and distilled water was added, the beaker was placed under an heat source for 5 mins. The compound was allowed to cool down for 10 min, the liquid was filtered off. A creamy shining crystals compound was gotten. And the compound was dried under sun 12g of Nitro-imidazole dissolve in dry ethanol with sodium metal, hydrogen sulphide (H_2S) was passed for 4hours at 60°C and it was reflux for 2hrs. The medium was neutralized with HCl in fume cupboard the solid was filtered 40ml of dry ethanol was poured in a 2 neck round bottom flask, add sodium metal, fused calcium chloride was poured in the connecting tube, HCl was poured in the separating funnel, Iron(II) sulphide was poured in the buckner funnel, the Nitro-imidazole was poured in the 2- neck round bottom flask and shaked together, more dry ethanol was added and mix thoroughly for 4 hrs. The compound was evaporated to dryness.

3.1.6. Refluxing: The brown compound was reflux for 8 hours, and distilled water was added to change it to Golden brown colour. With the aid of a dropping pipette, the reaction was neutralized with Conc. HCl to give a brown solution. This was allowed to settle and buckner funnel was used with vacuum pump for the filtration and the residue is then dried. The melting point of the thiol is 120°C

3.1.7. Synthesis of 1-methyl-4-nitro-imidazole-5-sulphonyl chloride: 20% of HCl was used, and 20ml of distilled water was poured in the 2 neck flask. The thiol was added into the 2 neck flask and 20ml of HCl was also added to the 2 neck flask. The flask was swirled for homogeneity and placed inside a water bath, this was set upon a tripod stand and the experiment was carried out in a fume Cupboard.

3.1.8 Generation Of Chlorine Gas Using Potassium Permanganate: Potassium permanganate was poured into a 1 litre conical flask and this was swirled, HCl was poured into the separating funnel and the separating funnel was clamped, the tap of the separating funnel was opened this was in a dropwise form into the potassium permanganate. The reaction was for 3hrs.and the product was 1-methyl imidazole-5-sulphonylchloride.

3.1.9 Synthesis of 1-methyl-4-nitro-5-N,N-diethylsulphonamide: Diethylamine was reacted with 1-methyl imidazole-5-sulphonylchloride to give 1-methyl-4- nitro-5-N,N-diethylsulphonamide

3.2 Antibacterial Screening

The synthesized compound (1-methyl-4-nitro-5-N,N-diethylsulphonamide) was screened for antibacterial test against four (4) bacterial, namely: *Salmonella Typhi, Escherichia coli, Staphylococcus aureus,* and *Shigella* using agar well diffusion method. 9g of Mueller Hinton Agar was dissolved in 200ml of water, nutrients broth (0.7grams) was measured and 50ml of water was added to it and this was stirred to dissolve. This was poured into 5 testubes and corked. Both the agar and the nutrients broth was sterilized using an autoclave at 121°C for 15mins. Plates were arranged and the Mueller Hinton Agar was poured into each plate allow to solidify and was labeled accordingly.

The microorganisms was transferred into the nutrients broth prepared in the five testubes according to the 4 microorganisms labelled above with the 5th one as a control which microorganism was not introduced and incubated for 15mins. Using swab stick the nutrient broth containing microorganism. The microorganisms were swab or smear on the plate containing solidified Mueller Agar. The plates were incubated at 37°C for 24 hrs after which the plate were observed for clear zone of inhibition. And the diameter of the inhibition zone was measured.

3.3 Antifungal Screening

The synthesized compound (1-methyl-4-nitro-5-N,N-diethylsulphonamide) was screened for antifungal activities on the pathogenic fungi, namely: *Candida albican, Aspergillus niger* using agar well diffusion method. The pure culture of *Candida albican and Aspergillus niger* were introduced into 10mls Potatoe dextrose agar (PDA) broth into two separate tubes and incubated at 25°C for 3 days after which the spores were smeared on PDA agar plate and allow to dry for 15 min after which it was bore with 6mm cork borer, and the compound was introduced into the bore holes 0.1m of the compound was introduced into the bore holes and DMSO was used as control and it was incubated at 25°C for 5 days and result was recorded.

4.0 Results and Discussion

4.1 Synthesis of N,N′-Dimethyl Oxamide

N,N′-Dimethyl oxamide was synthesized as shown in the figure 4.1 below. The methyloxamide was reacted with Phosphorus Pentachloride (PCl_5). The colour of the compound was brown.

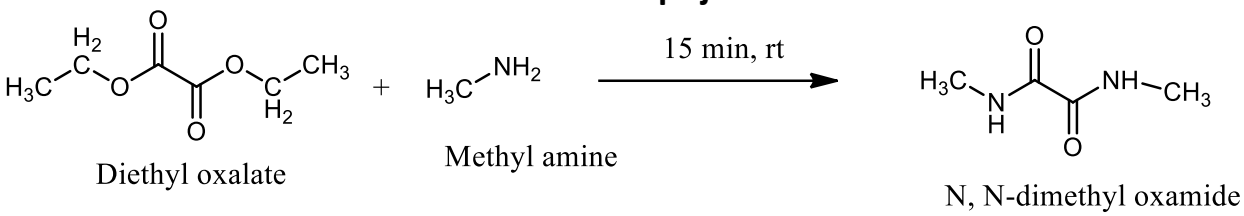

Figure 4.1 Synthesis of N, N′-Dimethyl Oxamide

4.2 Synthesis of 1-Methyl-5-Chloroimidazole

N, N′-Dimethyl oxamide was subjected to cyclisation reaction using phosphorus (V) chloride (figure 4.2) to form 1-Methyl-5-chloroimidazole. The compound was greenish yellow in colour.

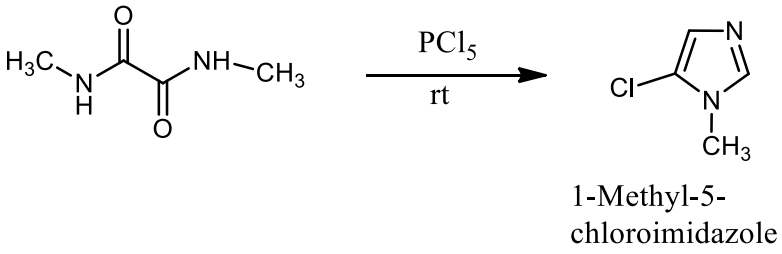

Figure 4.2: Synthesis of 1-Methyl-5-Chloroimidazole

4.3 Synthesis of 1-Methyl, 4-Nitro-5-Chloroimidazole

1-Methyl-5-chloroimidazole was made to undergo nitration reaction and nitro group was introduced to position 4 on the imidazole ring. The nitration of 1-Methyl-5-chloroimidazole led to the formation of 1-Methyl, 4-nitro-5-chloroimidazole as shown in the figure 4.3 below. The compound formed was a creamy coloured crystal

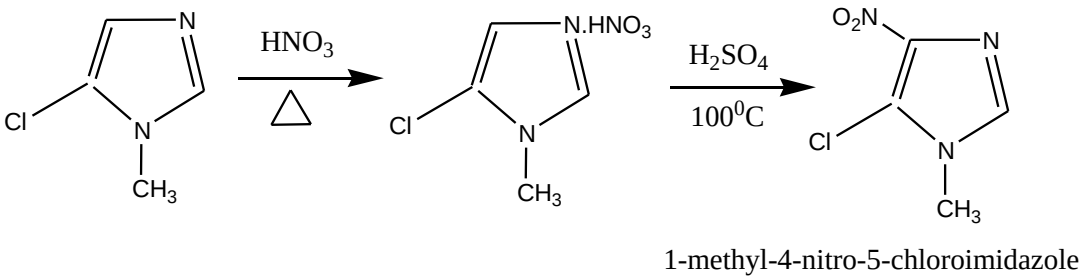

Figure 4.3: Synthesis of 1-Methyl, 4-nitro-5-chloroimidazole.

4.4 Synthesis of 1-Methyl, 4-Nitro-5-Thiolimidazole

1-Methyl-4-nitro-5-chloroimidazole was subjected to nucleophilic aromatic substitution reaction and halide at position 5 was replaced with thiol group to produce 1-Methyl, 4-nitro-5-thiolimidazole (figure 4.4). The compound was solid and brown in colour. Also, its melting point was 120 ^{o}C.

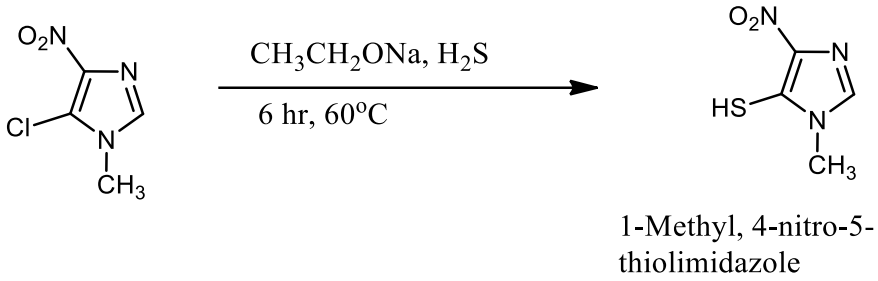

Figure 4.4 Synthesis of 1-Methyl, 4-nitro-5-thiolimidazole

4.5 Synthesis of 1-Methyl-4-Nitro-Imidazole-5-Sulphonyl Chloride

1-Methyl-4-nitro-5-thiolimidazole was transformed to 1-Methyl-4-nitro-imidazole-5-sulphonyl chloride and the thiol group at the position 5 and changed to sulphonyl chloride group (figure 4.5). The compound was light yellow and solid in nature.

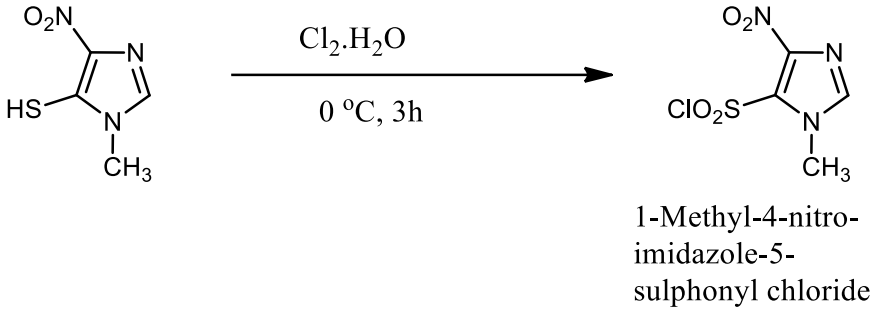

Figure 4.5: **Synthesis of 1-Methyl-4-Nitro-Imidazole-5-Sulphonyl Chloride**

4.6 Synthesis of 1-Methyl-4 Nitro-Imidazole-5 –N, N-Diethyl Sulphonamide

Diethyl amine was used to transform 1-Methyl-4-nitro-imidazole-5-sulphonyl chloride to 1-methyl-4 nitro-imidazole-5 –N, N-diethyl sulphonamide (figure 4.6). The sulphonyl chloride was changed to sulphonamide group. The properties of the compound was shown on the Table 4.1 below.

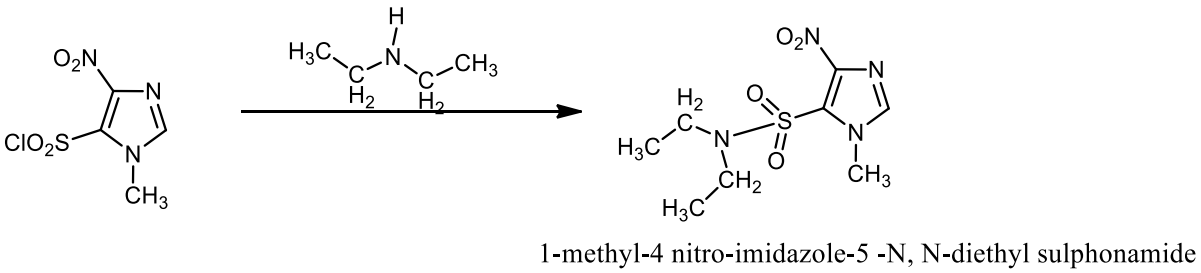

Figure 4.6: Synthesis of 1-methyl-4-nitro-imidazole-5-N, N-diethylsulphonamide

Table 4.1 Physical properties of 1-methyl-4-nitro-5-N, N-diethylsulphonamide

Properties	Results/Observation
Apperance	Oily
State	Liquid
Colour	Brown
TLC	Mobile phase = Chloroform
	Stationary phase = Silica gel
	R_f = 0.82

4.7 Antibacterial Screening

The antibacterial activity of 1-methyl-4-nitro-5-N,N-diethylsulphonamide was tested for against four organisms namely: *Salmonella Typhi, Escherichia coli, Staphylococcus aureus, Shigella* using agar well diffusion method. For the study of the biological activities of the compound. The inhibitory results are reported below in the table 4.2, it could be deduced that the compound possessed antibacterial properties perform better than all the bacteria. The table 4.2 shows the antibacterial activity of the compound synthesis.

Table 4.2 Results of Antibacterial screening

Bacteria	Compound
(mm)	(mm)
Staphylococcus Aureus	6
Escherichia Coli	2
Salmonella Typhi	1
Shigella	2

4.8 Antifungal Screening

The antifungal activity of 1-methyl-4-nitro-5-N,N-diethylsulphonamide was tested for against two (2) pathogenic fungi namely: *Candida albican, Aspergillus niger* using agar well diffusion method. For the study of the biological activities of the compound. The inhibitory results are reported below in the table 4.3, it could be deduced that the compound possessed antifungi properties. The table 4.3 shows the antifungi properties of the compound synthesis.

Table 4.3 Results of Antifungal Screening

Fungi	Compound
(mm)	(mm)

Fungi	Compound
(mm)	(mm)
Candida albican	3cm
Aspergillus niger	Resistance

5.0 Conclusion of the Study

In this study, authors found that imidazole derivatives show various activity against antimicrobial, anti-inflammatory, analgesic, antitubercular, anticancer etc. In addition, they also reported that the possible improvements in the activity can be further achieved by slight modifications in the substituents on the basic imidazole nucleus. The study further stressed that having structural similarity with histidine imidazole compound can bond with protein molecules with ease compared to the some other heterocyclic moieties. Thus imidazole offers better pharmacodynamic characteristics. Furthermore, some imidazole drugs, at high concentrations, could exert direct inhibitory effects on membranes, without interference with sterols and sterol esters. Various recent new drugs developments in imidazole derivatives show better effect and less toxicity. The compound 1-methyl-4-nitro-imidazole-5-N,N-diethylsulphonamide was synthesized in six stages reaction. Thin layer chromatography suggested synthetic transformation and also the methods used for the synthesis were established methods.1-methyl-4-nitro-5-N,N-diethylsulphonamideshowed moderate activities against Candida albican and its showed high activities against Staphylococcus Aureus.

6.0 Acknowledgement: My profound gratitude goes to my supervisor Dr. Owolabi Bodunde Joseph, for hisendless support and guidance towards my bachelor's degree project completed. I must acknowledge with gratitude the effort of my mentor Dr. Akintunde Ajagbe, Publisher and Editor in chief; Maryland Publishing and Research Institute, Inc. USA., for his powerful words of encouragement, guidance and most especially for making my dream of publishing this work come into fruition by funding the Publication. I am glad to be a member of your online mentoring program which has shaped me to become a better person in writing journal articles.

7.0 Reference of the Study

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