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Synthesis, Characterization and Antimicrobial Activity of *N*-Pyridin-3-yl-benzenesulfonamide

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Abstract

This study describes a simple one-pot synthesis of *N*-pyridin-3-yl-benzenesulfonamide and its antimicrobial activity. The reaction of benzene sulfonyl chloride with 3-aminopyridine in the presence of aqueous Na_2CO_3 and HCl as a scavenger furnished the sulfonamide in 93.3% yield. The structure of the synthesized compound was established using the spectral data obtained from FTIR, ^{1}HNMR and ^{13}CNMR). All spectrometric spectrum bands and peaks obtained were sulfonamide-related. The antibacterial test carried out against Gram-positive bacterium (*Staphylococcus aureus*) and Gram-negative bacteria (*Salmonella typhi and Eschericha coli*) tested upon at concentrations 150, 100, 50 and 25 mg/ml revealed that the synthesized *N*-pyridin-3yl-benzenesulfonamide possesses great antimicrobial activity.

1.0 Introduction

Sulfonamides, compounds with a general structural formula $RSO_2NHR^{/}$ where $R^{/}$ could H any organic group represents a very important group of compounds in both synthetic and medicinal chemistry [1]. Sulphonamides commonly referred to by many as 'sulfa drug' were the first therapeutic agents extensively used directly or indirectly as preventive and chemotherapeutic drugs against numerous diseases [1]. A large number of drugs with the sulfonamide moiety are already in wide clinical use; as antihypertensive agents [2], antibacterial [3], antiprotozoal [4], antifungal [5], anti-inflammatory [6], nonpeptidic vasopressin receptor antagonists [7] and translation initiation inhibitors [8]. Furthermore, other vital sulphonamide derivatives have been used as carbonic anhydrase

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inhibitors of commercial importance [9], and are also effective for the treatment of urinary, intestinal and ophthalmic infections, scalds, ulcerative colitis [2], rheumatoid arthritis [2,10], male erectile dysfunction as the phosphodiesterase-5inhibitor Sildenafil – better known under its commercial name, Viagra [2,11], and obesity [12]. More recently, sulphonamides have been employed as an anticancer agent [13], as the antiviral HIV protease inhibitor amprenavir and in Alzheimer's disease [2].

The discovery and formulation of the first Sulphonamide drug (Prontosil), unlocked a new age in medicine. This compound was first synthesized by Bayer chemists Josef Klarer and Fritz Mietzsch [14] as part of a research program initially designed for the synthesis of dyes with biological activities. The molecule was tested and in the late equinox of 1932 was found to be very effective in the treatment of some bacterial infections in mice by Gerhard Domagk, who in turn received the Nobel Prize in Medicine in 1939 [14]. A survey carried out in 2016 revealed that sulphonamides represented 15% of the top 100 most recommended drugs [14] for the therapeutic applications against cardiovascular, infectious, and neurological diseases [14]. In the agrochemical industry also, the sulphonamide motifs are incorporated in a variety of pesticides, including Asulam, Orzalin, Fomesafen, Halosafen, and Sulfentrazone [14].

There are various developed synthetic pathways to the production of Sulphonamides and its derivatives. The most common of them is the reaction of sulfonyl chloride and amine. This article reports the synthesis of *N*-pyridin-3-yl-benzenesulfonamide by reaction of the benzene sulphonyl chloride and the corresponding 3-aminopyridine, the characterization of the synthesized compound using FTIR and NMR spectrophotometry analysis and finally the evaluation of the antimicrobial activity of the synthesized compound.

2.0 Materials and Method

2.1 General

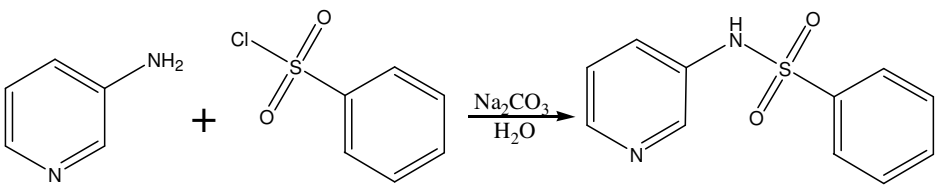
Chemicals used in this study were commercially analytical grade and were used as received. Chemicals used includes; 3-aminopyridine (JHD, 99.8%), Benzenesulphonyl chloride (BHD, 99%), Dimethylsulfoxide (BHD, 99%), Concentrated hydrochloric acid (JHD, 37%), Sodium trioxocarbonate (IV) (lubachemie 99%), Ethanol (JHD, 99%). Nuclear Magnetic Resonance (NMR) analysis of the compound was carried out using a JEOL-LA-400MHz NMR spectrophotometer with $CDCl_3$ used as internal standard at the University of Strathclyde. Fourier Transform Infrared Spectroscopy (FT-IR) analysis was

carried out using 8400SINFRARED Spectrophotometer, by employing KBr discs at NARIT Zaria.

2.2 Synthesis of N-Pyridin-3-yl-benzenesulfonamide

The procedure reported by Almarhoon *et al.* [15] with slight modification was adopted. A mixture of 3-aminopyridine (3.0 g, 0.032 mol) and benzene sulphonylchloride (3.0 mL, 0.032 mol) was gently introduced into a round bottom flask containing (25.0 mL, 2.0 M) Na_2CO_3 aqueous solution and stirred for 2 hours. The pH of the reaction was closely monitored and maintained at a high value of 8 – 10. At the end of the reaction, (2.0 M, 25.0 mL) HCl was slowly added to the reaction mixture to adjusted the pH to 2. The reaction mixture was then filtered to obtain the brown precipitates which were formed (Scheme 1). This crude product was washed repeatedly with distilled water and finally recrystallized from hot ethanol. The percentage yield was thus calculated using equation 1 and the melting point determined using a melting point apparatus (Scientech SE-175).

$$\% \; yield = \frac{Experimental \; yield}{Theoritical \; yield} \times 100 \tag{1}$$



Scheme 1. Synthetic pathway for *N*-pyridin-3-yl-benzenesulfonamide.

2.3 Characterization

The purified white crystals were subjected to both ^{1}HNMR and ^{13}CNMR spectroscopy using a JEOL-LA-400MHz NMR spectrophotometer with DMSO as internal standard at the University of Strathclyde. Fourier Transform Infrared Spectroscopy (FT-IR) analysis using FTIR-8400SINFRARED Spectrophotometer, employing a KBr discs at NARIT Zaria.

2.4 Antimicrobial screening

The antimicrobial screening of the synthesized compound and Ciprofloxacin (as control) were carried out using the well in agar (well diffusion) method as reported by Ike

et al. [16]. The already characterized gram positive bacterium (*Staphylococcus aureus*) and two-gram negative bacteria (*Salmonella typhi and Escherichia coli*) were resuscitated using selective mediums such as Tyrosine methylene blue agar (for *E.coli*) and nutrient agar (for others). Various concentrations (150-25 mg/ml) of the synthesized compound were prepared following the report of Akujobi *et al*. [17] and Ike *et al.* [16] using 30% Dimethylsulfoxide (DMSO). In order to achieve standard and uniformity in inoculation of the bacteria species, the McFarland standard was also prepared.

3.0 Results and Discussion

3.1 Results

Table1. Physicochemical characterization of synthesized compound.

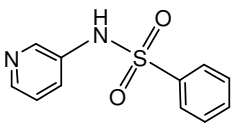
Properties	Values
Name	*N-Pyridin-3-yl-benzenesulfonamide*
Appearance	*Light brown crystalline solid*
Molecular mass	*234.273g/mol*
yield	*2.8g, 93.3 %*
Melting point	*160-162^{o}C*
Structure	

Table 2. FTIR absorption bands of synthesized compound.

S/N	Functional group	Vibration frequency (cm^{-1})	
		Sample	*Ref Values
1	N-H	3664.67	3350 – 3310
2	C=C	1481.32, 1519.96& 1573.97	1650 – 1566
3	C-N	1026.16	1250 – 1020
4	C=N	1651.12	1690 – 1640
5	S=O	1350.22	1370 – 1335
6	C-H	3009.05 &2877.89	3000-2500

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Table 3. [1]HNMR signals of the synthesized compound.

Positions	Experimental	ChemDraw software analysis
	126 MHz, DMSO, (δ ppm)	DMSO, (δ ppm)
1	7.61 (d, 1H, -CH)	7.26 (d, 1H, -CH)
3	7.83 (s, 1H, -CH)	8.53 (d, 1H, -CH)
4	7.63 (d,1H, -CH)	8.23 (d, 1H, -CH)
5	7.50 (t, 1H, -CH)	7.40 (t, 1H, -CH)
7	8.29 (s, 1H, -NH)	4.00 (s, 1H, -NH)
10 & 14	7.55 (d, 1H, -CH)	7.93 (d, 1H, -CH)
11 & 13	7.29 (t, 1H, -CH)	7.54 (t, 1H, -CH)
12	7.78 (t, 1H, -CH)	7.30 (t, 1H, -CH)

Table 4. [13]CNMR signals of the synthesized compound

Positions	**Experimental**	**ChemDraw software analysis**
	126 MHz, DMSO, (δ ppm)	DMSO, (δ ppm)
1	145.23 (-C=N)	137.90 (-C=N)
3	141.66 (C-C-N)	139.00 (C-C-N)
4	124.02 (-C-CH)	124.50 (-C-CH)
5	127.51 (-C-C-CH)	121.50 (-C-C-CH)
6	129.41 (-C-NH)	145.10 (-C-NH)
9	139.02 (-C-S)	139.30 (-C-S)
10 & 14	128.05 (-C-C-S)	125.50 (-C-C-S)
11 & 13	129.41(CH-C-CH)	128.80(CH-C-CH)
12	133.19 (CH-C-CH)	131.70 (CH-C-CH)

Table 5. Antimicrobial activity of *N*-pyridin-3yl-benzenesulfonamide and ciprofloxacin.

Sample	Concentration (ppm)	Average zone of inhibition (mm)		
		Gram negative bacteria		Gram positive bacteria
		E. coli	*S.typhi*	*S.aureus*
N-pyridin-3yl-benzenesulfonamide	150	12	16	14
	100	8	12	10
	50	-	8	5
	25	-	5	-
Ciprofloxacin (control)	150	16	26	32
	100	12	24	28
	50	8	18	22
	25	-	16	18

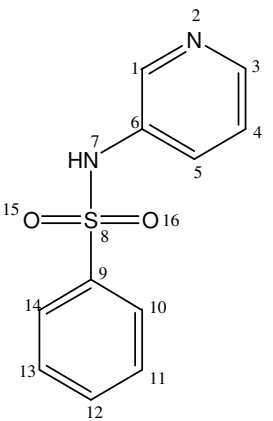

Figure 1. Numbered structure of *N*-pyridin-3yl-benzenesulfonamide.

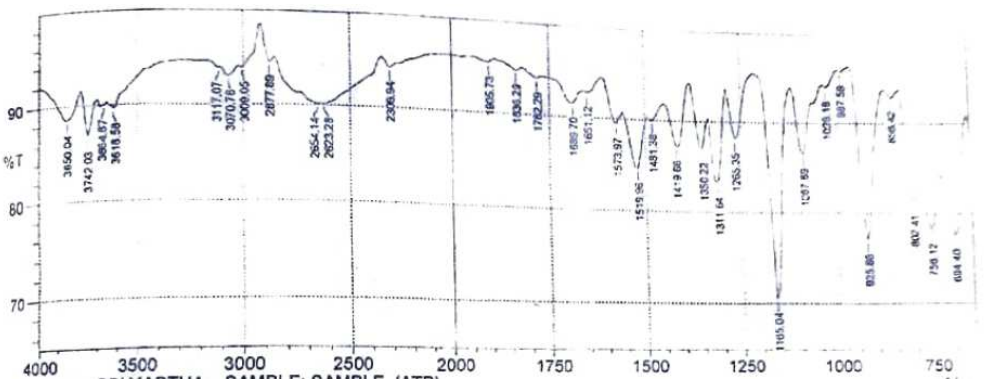

Figure 2. FTIR spectrum of *N*-pyridin-3yl-benzenesulfonamide.

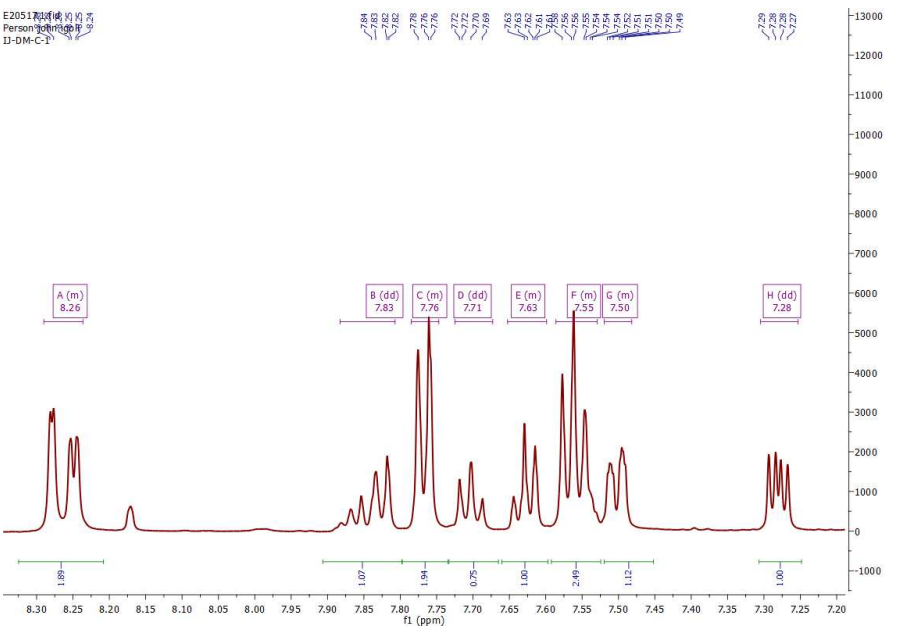

Figure 3. [1]H NMR spectrum of *N*-pyridin-3yl-benzenesulfonamide.

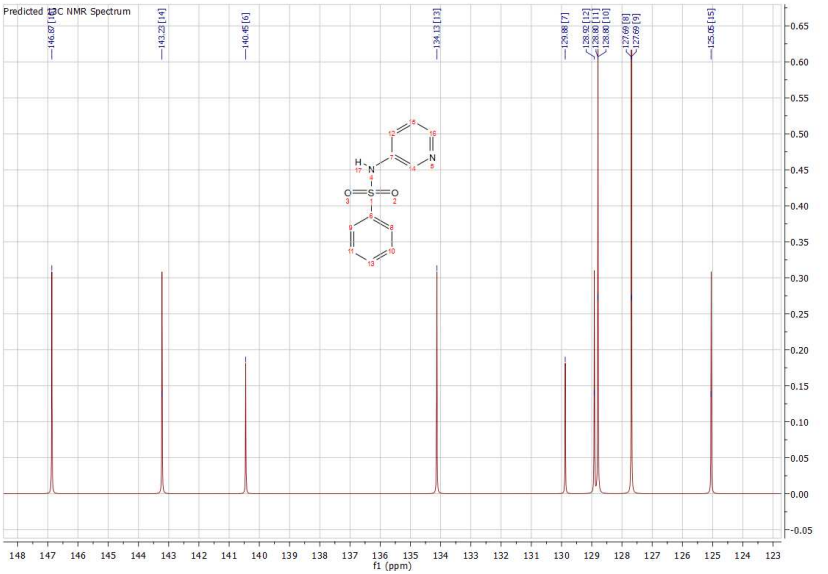

Figure 4. ^{13}C NMR spectrum of *N*-pyridin-3yl-benzenesulfonamide.

3.2 Discussion

N-Pyridin-3-yl-benzenesulfonamide, a light brown crystalline solid was synthesized in the presence of Na_2CO_3 by a facile one-pot reaction of 3-aminopyridine with benzene sulfonyl chloride. It was produced at a high yield of 93.3 %, which is consistent with the findings of Ijeomah *et al.* [1].

The melting temperature of the synthesized compound was also found to be between 160 – 162^{o}C (Table 1) using a melting point apparatus. The synthesised product was also subjected to FTIR analysis, and the spectrum data obtained (Figure 2, Table 2) revealed a characteristic absorption band at 1350.22 cm^{-1}, which corresponds to a sulphonamide's S=O stretch vibration, 1026.16 cm^{-1}, which reveals a C-N aromatic amine stretch vibration, 1651.12 cm^{-1}, which corresponds to an aromatic compound's C=N stretch vibration. The only one band at 3664.67 cm^{-1} which corresponds to N-H stretch vibration showed that the product is a secondary amine and 3009.05 cm^{-1} corresponding to the C-H stretch vibrations of the aromatics.

The ^{1}HNMR spectra of the synthesised compound (Figure 3, Table 3) revealed a singlet peak at 7.88 and 8.29 respectively for the NH proton and the N-C-CH=N (positions 3 and 8 respectively). Doublet peaks were observed at 7.55, 7.61 and 7.63 corresponding to the CH protons at positions 10 & 14, 1 and 4 respectively (Figure 1).

Triplet peaks at 7.29, 7.50 and 7.78 were also observed for the CH protons at positions 11 & 13, 5 and 12 respectively (Figure 1).

^{13}CNMR spectra (Figure 4, Table 4) revealed peaks at 145.23, 141.66, 124.02, 127.51, 129.41, 139.02, 128.05, 129.41 and 133.19 ppm which corresponds to carbon atoms at positions 1, 3, 4, 5, 6, 9, 10 & 14, 11 & 13 and 12 respectively (Figure 1). Both the ^{1}H and ^{13}CNMR spectrum findings are consistent with prior observations [1,10-11].

The result (Table 5) of the biological activity of the synthesized N-pyridin-3yl-benzenesulfonamide against gram-positive bacterium (*Staphylococcus aureus*) and gram-negative bacteria (*Salmonella typhi and Escherichia coli*) tested upon at concentrations 150, 100, 50 and 25 mg/ml revealed that the synthesized N-pyridin-3yl-benzenesulfonamide possesses great antimicrobial activity against all tried bacteria. The highest antibacterial activity was observed against *Salmonella typhi* at a concentration of 150 – 25 mg/ml which gave an average inhibiting zone of 16, 12, 8, and 5 mm respectively. Average inhibiting zones of 14, 10 and 5 mm at concentrations 150, 100 and 50 mg/ml respectively was observed when tried against *Staphylococcus aureus.* No average zone of inhibition was seen for concentration 25 mg/ml. The weakest antibacterial activity was observed against *Escherichia coli,* with poor average zones of inhibitions of 12 and 8 mm observed at concentrations 150 and 100 mg/ml respectively. Whereas, no average zone of inhibition was observed at concentrations 50 and 25 mg/ml.

4.0 Conclusion

The sulfonamide, *N*-pyridin-3yl-benzenesulfonamide was successfully synthesized and characterised using the spectral data obtained from FTIR, ^{1}H NMR and ^{13}C NMR spectroscopic analyses. The results obtained showed peaks similar to the ones in literature for sulfonamides. This synthesized compound also show great potential as a possible candidate for future antimicrobial agent as revealed by the result of the antimicrobial screening carried out. Also, the easy synthetic route and the high yield of N-pyridin-3yl-benzenesulfonamide makes it an attractive alternative to pharmaceutical industries seeking new lead compounds.

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