Vol. 1 No. 2, December 2021

FUAM Journal of Pure and Applied Science

Available online at
www.fuamjpas.org.ng

An official Publication of
College of Science
Joseph Sarwuan Tarka University,
Makurdi.

FUAM Journal of Pure and Applied Science
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https://fuamjpas.org.ng/
Vol.1. No. 2. December, 2021

One Pot Facile Synthesis and Characterization of 2-(Phenyl-2-sulfonylamino)-6-methylpyridine

*A.O. Ijeomah, D.C. Ike and J.O. Odoh
Department of Chemistry, Joseph Sarwuan Tarka University, Makurdi, P.M.B 2373, Benue State, Nigeria.
*Correspondence E-mail: tinaijeomah@gmail.com

Received: 11/10/2021 Accepted: 25/10/2021 Published online: 08/11/2021

Abstract
This research reports a one-pot facile synthesis of 2-(phenyl-2-sulfonylamino)-6-methylpyridine. The sulfonamide was synthesized from the reaction of benzene sulfonyl chloride and 2-amino-6-methylpyridine in the presence of aqueous Na_2CO_3 serving as an HCl scavenger. The synthesized compound was obtained at a yield of 78 %. The synthesized product was structurally elucidated using data obtained fromFourier Transform Infrared Spectrometer (FTIR) and Nuclear Magnetic Resonance spectrometer (^{1}H NMR and ^{13}C NMR). FTIR spectrum showed bands at 3232.80, 1442.08, 1522.08, 1604.83,1273.06, 1705.13, 1365.65 and 2955.04 cm^{-1}, ^{1}H NMR spectrum peaks were observed at δ7.88, 7.85, 7.84, 7.62, 7.54, 7.51, 7.50 and 2.31ppm and ^{13}C NMR spectrum peaks were seen at δ154.91, 151.92, 143.91,141.91, 132.24, 126.97,129.33, 113.97,and 111.56 ppm. All spectrometric spectral bands and peaks obtained corresponded to those of sulfonamides.

Keywords: Synthesis, Characterization, Sulfonamide, 2-(phenyl-2-sulfonylamino)-6-methylpyridine benzenesulfonyl chloride.

Introduction

Sulfonamides are compounds with the general molecular formula RSO_2NH_2 where R is an organic moiety. It constitutes a group of essential compounds in both synthetic and medicinal chemistry [1]. The functionality of the sulfonamides constitutes the structural motif of various drugs and compounds endowed with antimicrobial, antitumor, anti-inflammatory, hypoglycemics, antipsychotic, anticancer, and protease inhibitor activity among other biological activities [2]. The discovery and commercialization of Prontosil [3] in 1935 as a drug, birthed immense researches on syntheses of various sulfonamide derivatives and their biological applications [4–5]. Various synthetic pathways have been established for the synthesis of sulfonamide [6]. Examples include the use of sulfonyl chloride and amines [7], use of a chlorinating agent with the desirable sulphurated precursor [8], use of non-conventional methods such as transition metals [9] or Grignard reagents [10], C–H activation, flow-based technology, telescoped, solid-phase synthesis, and many others [11]. All these methods though very useful have some drawbacks and prompted the continued search for improved routes to their syntheses. The search for a simple and effective synthetic method for novel sulfonamides is still of great concern to researchers all over the world even as chemists are trying to use fewer organic solvents as reaction mediums and at the same time generate as little waste as possible [12-14]. The most common synthetic route to sulfonamide is the direct reaction of sulfonyl chlorides and amines as starting materials, involving the scavenging of the generated HCl with organic solvents and organic amine bases [11,15]. Another protocol is the modified Schotten–Baumann conditions [16], in which a two-phase system of organic solvents and basic aqueous solution (Na_2CO_3 or NaOH) is used [14]. A facile, eco-friendly method for sulfonamide, amino acid and sulfonate acid synthesis has been reported from the reaction of its sulfonyl chloride and amino acid using water as solvent andNa_2CO_3 as HCl scavengers at room temperature [14,17].

Reported herein, is a one-pot facile synthetic pathway for the synthesis of 2-(phenyl-2-sulfonylamino)-6-methylpyridine from the reaction of 2-amino-6-methylpyridine and the corresponding sulfonyl chloride in the presence of Na_2CO_3 as HCl scavenger at room temperature while employing water as the reaction medium.

Materials and Methods

General

Chemicals used in this study were commercially analytical grade and were used as received. Chemicals used includes; 2-amino-6-methylpyridine (JHD, 99.8%), Benzenesulfonylchloride (BHD, 99%), Concentrated hydrochloric acid (JHD, 37%), Sodium trioxocarbonate (IV) (lubachemie 99%), Ethanol (JHD, 99%). Nuclear

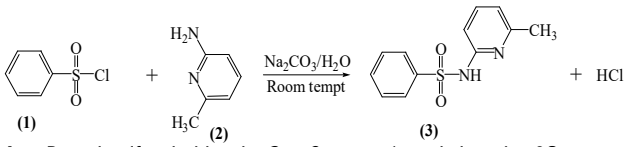
Magnetic Resonance (NMR) analysis of the compound was carried out using a JEOL-LA-400MHz NMR spectrophotometer, while $CDCl_3$ was used as internal standard at the University of Strathclyde. Fourier Transform Infrared Spectroscopy (FT-IR) analysis was carried out using 8400SINFRARED Spectrophotometer, by employing KBr discs at NARIT Zaria.

Synthesis of 2-(phenyl-2-sulfonylamino)-6-methylpyridine

The synthetic route reported by Almarhoon *et al.,* [14] was adopted with slight modifications. A mixture of 2-amino-6-methylpyridine (.2.5 g, 0.02 mol) and benzene sulfonylchloride (4.9 mL, 0.02 mol) was gently emptied into a flat bottom flask containing 30 mL of 1.0 M Na_2CO_3aqueous solution and stirred for 3 hours. The pH of the reaction was closely monitored and at completion of the reaction concentrated HCl (0.5 mL) was added slowly to the reaction to adjusted the pH to 2. The reaction mixture was then filtered to obtain the white precipitate which was formed. This crude product was washed repeatedly with distilled water and finally recrystallized from hot ethanol (Scheme 1). The percentage yield was thus calculated using equation I and the melting point determined using a melting point apparatus (Scientech SE-175).

$$\%\ yield = \frac{Experimental\ yield}{Theoritical\ yield} \times 100 \qquad (I)$$

I = Benzyl sulfonyl chloride, **2** = 2-amino-6-methylpyridine and **3 =** 2-(phenyl-2-sulfonylamino)-6-methylpyridine



I = Benzyl sulfonyl chloride, **2** = 2-amino-6-methylpyridine**&3 =** 2-(phenyl-2-sulfonylamino)-6-methylpyridine

Scheme 1. Reaction pathway for the synthesis of 2-(phenyl-2-sulfonylamino)-6-methylpyridine

Characterization

The synthesized compound was characterized using FTIR spectrophotometer, ^{1}HNMR and ^{13}CNMR spectrophotometer.

Results and Discussion

Results

The results from the different characterization carried out are presented in this order:

Table 1: Physicochemical characterization of synthesized compound

Table 2: FTIR absorption bands of 2-(phenyl-2-sulfonylamino)-6-methylpyridine

Table 3:^{1}HNMR resonance signals of 2-(phenyl-2-sulfonylamino)-6-methylpyridine

Table 4: ^{13}CNMR resonance signals of 2-(phenyl-2-sulfonylamino)-6-methylpyridine

Figure 1.^{1}H NMR spectrum of 2-(phenyl-2-sulfonylamino)-6-methylpyridine

Figure 2.^{13}C NMR spectrum of 2-(phenyl-2-sulfonylamino)-6-methylpyridine

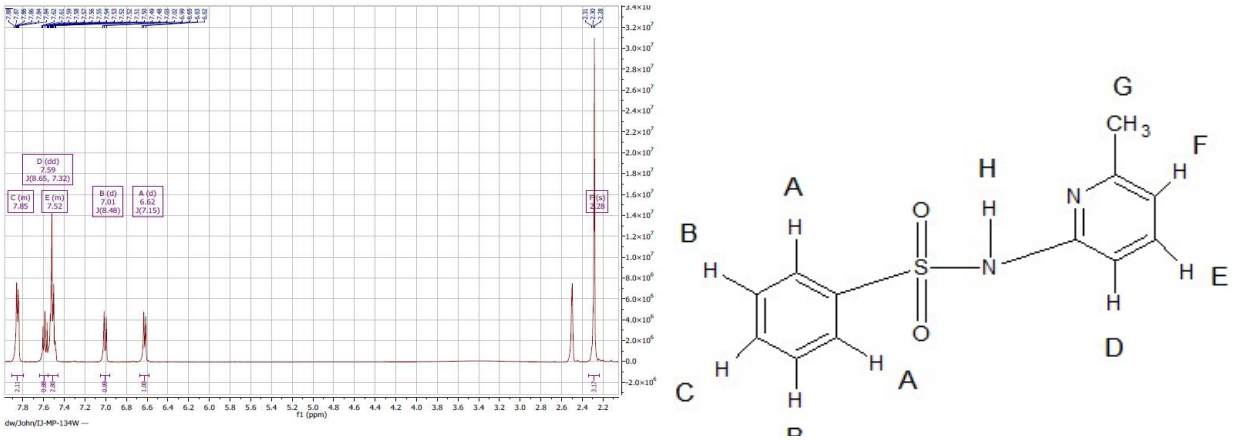


Figure 1. ^{1}H NMR spectrum of 2-(phenyl-2-sulfonylamino)-6-methylpyridine

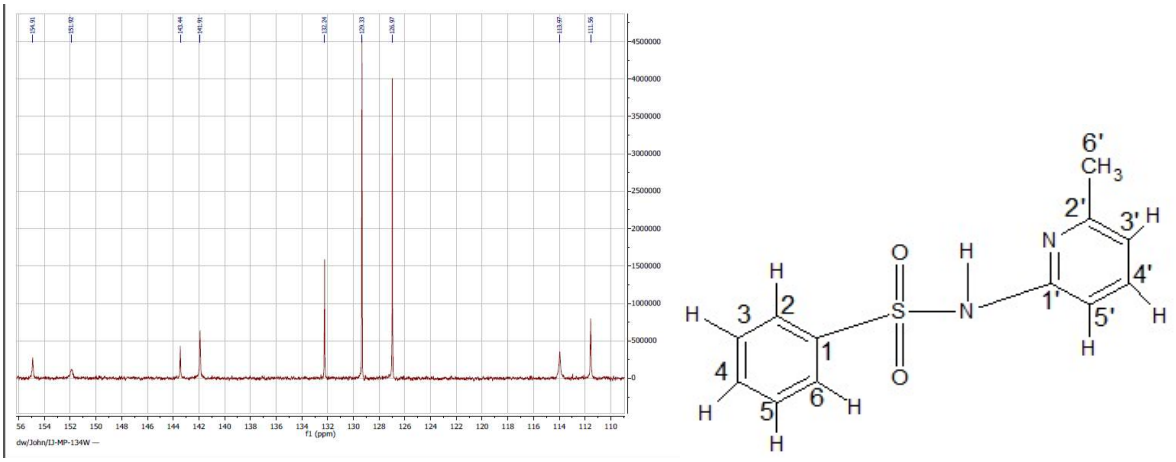


Figure 2. ^{13}C NMR spectrum of 2-(phenyl-2-sulfonylamino)-6-methylpyridine

Table1: Physicochemical characterization of synthesized compound

Properties	Values
Name	2-(phenyl-2-sulfonylamino)-6-methylpyridine
Appearance	*White powder*
yield	*4.5g,78%*
Melting point	*134-136 °C*

Table 2: FTIR absorption bands of synthesized compound

S/N	Functional group	Vibration frequency (cm^{-1})	
		Sample	Ref. Values
1	N-H	3232.80	3350 – 3310
2	C=C	1442.08,1522.08 and 1604.83	1650 - 1566
3	C-N	1273.06	1250 - 1020
4	C=N	1705.13	1690 – 1640
5	S=O	1365.65	1370 - 1335
6	C-H	2955.04	3000-2500

Table 3: ^{1}HNMR resonance signals of the synthesized compound

Positions	Experimental	ChemDraw software analysis
	400 MHz, $CDCl_3$, (δ ppm)	DMSO, (δ ppm)
A	7.88 (d,1H, -CH)	7.93 (d, 1H, -CH)
B	7.85 (t, 1H, -CH)	7.54 (t, 1H, -CH)
C	7.84 (t, 1H, -CH)	7.30 (t, 1H, -CH)
D	7.62 (d, 1H, -CH)	6.54 (d, 1H, -CH)
E	7.54 (t, 1H, -CH)	7.43 (t, 1H, -CH)
F	7.51 (d, 1H, -CH)	6.49 (d, 1H, -CH)
G	7.50 (s, 3H, $-CH_3$)	2.55 (s, 3H, $-CH_3$)
H	2.31 (s, 1H, -NH)	4.00 (s, 1H, -NH)

Table 4: ^{13}CNMR resonance signals of the synthesized compounds

Positions	Experimental	ChemDraw software analysis
	400 MHz, $CDCl_3$, (δ ppm)	DMSO, (δ ppm)
1	143.44 (-C-S)	139.30 (-C-S)
1'	154.91 (-C-N)	160.70 (-C-N)
2,6	126.97(-2CH-)	125.50 (-2CH-)
2'	151.92 (-C-CH_3)	157.70 (-C-CH_3)
3,5	129.33(-2CH-)	128.80 (-2CH-)
3'	113.97 (-CH-)	112.40 (-CH-)
4	132.24(-CH-)	131.70 (-CH-)
4'	141.91 (-CH-)	138.2(-CH-)
5'	111.56 (-CH-)	105.9(-CH-)
6'		20.9 ($-CH_3$)

Discussion

The sulfonamide, 2- (phenyl-2-sulfonylamino) -6-methylpyridine was synthesized in the presence of Na_2CO_3 by the simple reaction of 2-amino-6-methylpyridine with benzene sulfonyl chloride. It was obtained in great yield of 78 % which is similar to the report of Rehman *et al* [15].

The melting point of the compound was also determined to be 134-136^{O}C (Table 1). The synthesized product was also subjected to FTIR analysis and the spectrum data obtained (Table 2), showed a characteristic absorption band at 1365.65 cm^{-1} which corresponds to S=O stretch vibration of a sulfonamide, 1273.06 cm^{-1} which reveals a C-N aromatic amine stretch vibration, 1604.83 cm^{-1} which correspond to C=C stretch vibration of an aromatic compound, 1705.13 cm^{-1}corresponding to C=N stretch vibration, 3232.80 cm^{-1} which corresponds to the N-H stretch of a secondary amine, 1982.89 $cm^{-1}$for a C-H aromatic stretch vibration and 2955.06 cm^{-1} for C-H stretch vibration of the methyl group.

The ^{1}H NMR spectra (Figure 1, Table 3) of the synthesized compound showed a doublet peak at δ7.88, 7.62 and 7.51related to the aromatic protons at positions 'a, d & f' (Ha, Hd and Hf) respectively, triplet peak at δ7.85, 7.84 and 7.54 corresponding to the aromatic protons at positions 'b, c & e' (Hb, Hc and He) respectively. A singlet peak at δ 7.50 and 2.31 corresponding to the amine hydrogen and the three methyl hydrogens (Hh and Hg) respectively. ^{13}C NMR spectra (Figure 2, Table 4) showed a peak at δ154.91, 151.92,143.91,141.91, 132.24, 113.97, and 111.56 ppm for $C_{1'}$, $C_{2'}$,C_{1}, $C_{4'}$, C_4, $C_{3'}$, and $C_{5'}$respectively, 126.97 ppm for $C_2$and C_6 respectively, and a peak at δ 129.33 for C_3 and C_5 respectively. The spectral data from the ^{1}H NMR and the ^{13}C NMR both conforms to previous reports [2,14-15].

Conclusion

The sulfonamide, 2-(phenyl-2-sulfonylamino)-6-methylpyridine was synthesized via a one pot facile reaction of benzene sulfonyl chloride and 2-amino-6-methylpyridine in the presence of aqueous Na_2CO_3 serving as HCl scavenger. The structure of the synthesized compoundwas confirmed by the spectral data obtained from FTIR, ^{1}H NMR and ^{13}C NMR spectroscopic analyses

which showed peaks similar to the ones in literature for sulfonamides.

Acknowledgement
The Authors acknowledge the support of **Prof. J.O. Igoli** in running the NMR Analysis.

Declaration of conflicting interests
The authors declared no potential conflicts of interest

References

[1] Das, T. C., Quadri, S. A., & Farooqui, M. 2018, Recent advances in synthesis of sulfonamides: A review. *Chemistry & Biology Interface*, 8(4):194-204

[2] Orie J.K.,Ike D.C. and Nzeneri J.U. 2021, Synthesis and Characterization ofMetal Complexes with 4-Methyl-*N*-(*p*-methylphenylsulphonyl)-*N*-(pyridin-2-yl)benzeneSulphonamide.*ModernChemistry*.9(3): 46-51,doi: 10.11648/j.mc.20210903.11

[3] Török E, Moran E, and Cooke F. 2016, Oxford handbook of infectious diseases and microbiology. Oxford University Press

[4] Stokes, S. S., Albert, R., Buurman, E. T., Andrews, B., Shapiro, A. B., Green, O. M., ... & Otterbein, L. R. 2012, Inhibitors of the acetyltransferase domain of N-acetylglucosamine-1-phosphate-uridylyltransferase/glucosamine-1-phosphate-acetyltransferase (GlmU). Part 2: optimization of physical properties leading to antibacterial aryl sulfonamides. *Bioorganic & medicinal chemistry letters*, *22*(23): 7019-7023

[5] Pokhrel L., Maezawa I., Nguyen T.D., Chang K.O., Jin L.W. and Hua D.H. 2012, Inhibition of Acyl-CoA: Cholesterol acyltransferase (ACAT), overexpression of cholesterol transporter gene, and protection of amyloid β (Aβ) oligomers-induced neuronal cell death by tricyclic pyrone molecules. *Journal of medicinal chemistry* 55(20):8969-73

[6] Maleki B., Hemmati S., Tayebee R., Salemi S., Farokhzad Y., Baghayeri M., Zonoz F.M., Akbarzadeh E., Moradi R., Entezari A. and Abdi M.R.2013, One□Pot Synthesis of Sulfonamides and Sulfonyl Azides from Thiols using Chloramine□T. *Helvetica Chimica Acta*. 96(11):2147-51

[7] Jafarpour M., Rezaeifard A. andHeidari M. 2011, Efficient organic transformations mediated by $ZrOCl_2 \cdot 8H_2O$ in water. Phosphorus, Sulfur, and Silicon and the Related Elements. 186(7):1470-82

[8] Veisi H., Ghorbani-Vaghei R., Hemmati S. and Mahmoodi J. 2011,Convenient one-pot synthesis of sulfonamides and sulfonyl azides from thiols using N-chlorosuccinimide. *Synlett*.11(16):2315-20

[9] Flegeau, E.F. Harrison, J.M. and Willis, M.C. 2016, One-Pot Sulfonamide synthesis exploiting the palladium-catalyzed sulfination of aryl iodides. *Synlett*, 27,101–105

[10] Woolven H., González-Rodríguez C., Marco I., Thompson A.L. and Willis M.C. 2011, DABCO-bis (sulfur dioxide), DABSO, as a convenient source of sulfur dioxide for organic synthesis: utility in sulfonamide and sulfuramide preparation. *Organic letters* 13(18):4876-8

[11] Mondal S and Malakar S. 2020,Synthesis of sulfonamide and their synthetic and therapeutic applications: Recent advances. *Tetrahedron* 10:131662-18

[12] Pandya R., Murashima T., Tedeschi L. and Barrett A.G. 2003, Facile one-pot synthesis of aromatic and heteroaromatic sulfonamides. *The Journal of organic chemistry*68(21):8274-6

[13] Al Musaimi O., Jad Y.E., Kumar A., El-Faham A., Collins J.M., Basso A., de la Torre B.G. andAlbericio F. 2018, Greening the solid-phase peptide synthesis process. 2-methf for the incorporation of the first amino acid and precipitation of peptides after global deprotection. *Organic Process Research & Development* 22(12):1809-16

[14] Almarhoon Z., Soliman S.M., Ghabbour H.A.and El-Faham A. 2019, A Facile and Eco-Friendly Method for the Synthesis of Sulfonamide and Sulfonate Carboxylic Acid Derivatives—X-ray Structure, Hirshfeld Analysis and Spectroscopic Characterizations. *Crystals*9(1):35-40

[15] Rehman H., Abdul Qadir M., Shad H.A. and Khan Z.I. 2017,One Pot Synthesis of Some Novel Sulfonamide Derivatives Containing -NH2 Group: Spectral Characterization and Biological Evaluation. *Journal of Medicinal Chemistry* 7: 252-256

[16] Low C.M., Broughton H.B., Kalindjian S.B. and McDonald I.M. 1992,Novel oxathiazinones as gastrin ligands: Unexpected preducts from the schotten-baumann reaction of arylsulphonyl chlorides with derivatives of aspartic acid. *Bioorganic & medicinal chemistry letters*2(4):325-30

[17] Deng X.and Mani N.S. 2006,A facile, environmentally benign sulfonamide synthesis in water. *Green Chemistry*8(9):835-8

[18] Prior A.M., Gunaratna M.J., Kikuchi D., Desper J., Kim Y., Chang K.O., Maezawa I., Jin L.W. and Hua D.H. 2014, Syntheses of 3-[(Alkylamino) methylene]-6-methylpyridine-2, 4 (1H, 3H)-diones, 3-Substituted 7-Methyl-2H-pyrano [3, 2-c] pyridine-2, 5 (6H)-dione Fluorescence Probes, and Tetrahydro-1H, 9H-2,10-dioxa-9-azaanthracen-1-ones.*ynthesis*46(16):2179-90

Cite this article

Ijeomah A.O., Ike D.C. and Odoh J.O. (2021). One Pot Facile Synthesis and Characterization of 2-(Phenyl-2-sulfonylamino)-6-methylpyridine. FUAM Journal of Pure and Applied Science, **1**(**2**):84-88