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# Synthesis of New Paratoluene Sulphonamide Derivatives of Amino Acids And Their Anti Bacterial Activities

Ikpa Chinyere B.C[1,*] And Okoro Uchechukwu .C. [2,]
[1]*Department of Chemistry, Imo State University Owerri, Nigeria*
[2]*Department of Chemistry, University of Nigeria, Nsukka, Nigeria.*

***Abstract:*** *The synthesis of Para-toluene sulphonamides [3a-3e] was obtained by reacting P-Toluene sulphonylchloride with primary amine functionalities of five amino acids [1a-1e] in alkaline medium at the temperature below $0^0$C. Structures of all the newly synthesised compounds were analysed with FT-IR, $^1$H and $^{13}$C NMR and elemental analysis. Anti bacterial of the titled compounds were screened and the compounds exhibited potent anti bacterial properties.*

***Key words:*** *Para-toluene, sulphonamides, elemental analysis, anti-bacterial.*

## I. Introduction

Sulphonamides are widely used in medicinal chemistry because of their low cost, low toxicity and excellent biological activities [1] Recently, many synthetic methods have been reported for the preparation of sulphonamides [2] and these has led to the synthesis of new sulphonamide derivatives as drugs for clinical uses. Some of these sulphonamide derivatives from substituted benzene sulphonyl chlorides and their derivatives have shown potent anti microbial properties [3]. Apart from anti microbial properties, sulphonamides have been found useful in the treatment of burnt using mefenide [4], asthma using N-pentyl-N-(4,5-dibromo-2-methoxyphenyl)benzene sulphonamide [5]. Other sulphonamide drugs used in clinical treatments are Indisulam used in the treatment of multiple tumour types, most prominently in colon and lung cancer [6], Sulfasalazine used in the treatment of rheumatic arthritis [7], Spironolactone used as birth control drug [8] and Zonisamide used as an anti-convulsant sulphonamide [9].

Amino acids are useful dietary supplements that have a very important role in human immune status [10]. Due to allergies, complications and resistance of sulphonamide drugs which have been a common clinical problem that has been unabated, the aim of this research was to synthesise new sulphonamide drugs that is likely to be more effective and toxic free with amino acids which will help to boast human immune statue.

## II. Materials And Methods

### 2.1 General procedure as described by Furniss *et al* [11] for synthesis of Para-Toluene sulphonamides [3a-3e]

$Na_2CO_3$ (2.785 g, 26.25 mmol) was added to a solution of amino acid [**1a-1e]** (12.5 mmol) in $H_2O$ (15 ml) at -5˚C to 10$^o$C, followed by addition of p-Toulenesulphonyl chloride **[2]** (2.86 g, 15 mmol) in three portions over a period of 1h. The slurry was warmed to room temperature and allowed to stir for 4h. Upon completion of the reaction which was monitored with TLC using $CHCl_3/CH_3OH$ solvent system (9:1). The reaction mixture was acidified with 20% concentrated aqueous HCl solution to pH2, after which crystallization occurred and the product was obtained via suction filtration. The filtered crude product was washed with tartaric acid of pH2.2 buffer and dried in a vacuum oven at 60˚C for 12h to obtain Para-toluene sulphonamides (3a-3e) in good to excellent yield (70.21%-98%).

**2-[4-methylphenylsulphonamido] propanoic acid (3a)**

The amino acid is alanine **[1a]**. The molecular formula is $C_{10}H_{13}NO_4S$, Weight is 240.06, Theoretical yield is 3.00g, experimental 2.30g (76.67%), $R_f$ 0.76 and mp. 120-121$^0$C. **FT-IR(KBr)(cm$^{-}$1);** 1162.15 (S=O), 3426.66 (-NH-)3275.24 (-OH-)1520.92 (Ar) 1433.16 ($CH_3$ st), 1706.09 (C=O), **$^1$H NMR;** 1.13-1.15(3Hd, J.2.96,$CH_3$), 2.28(3Hs. J.3.27, Ar-$CH_3$), 3.72-3.76(1Hs.J.1.03, CH), 4.35 (-NH- dwarf), 8.02-8.04 (-OH-J.1.00), 7.15(1Hd.J. 0.30 Ar-H), 7.36(1Hd.J.2.03, Ar-H), 7.54(1Hd. J.0.24, Ar-H), 7.69 (1Hd. J.2.05, Ar-H). **$^{13}$C NMR;**145.41$_{C1}$, 143.92$_{C2}$, 126.92$_{C3}$, 138.88$_{C4}$, 125.98$_{C5}$, 129.91$_{C6}$, 21.38$_{C7}$, 178.70$_{C1'}$, 51.36$_{C2'}$, 18.86$_{C3'}$.

**2-[4-methylphenylsulphonamido] acetic acid [3b]**

The amino acid is glycine**[1b]** . The molecular formula is $C_9H_{11}NO_4S$, Weight is 229.25, Theoretical yield is 2.87g, experimental, 2.52g (87.80%), $R_f$ 0.71 and mp. 114-115$^0$C. **FT-IR(KBr)(cm$^{-1}$);** 1140.83(S=O), 1530.57(-$CH_3$-), 3361.07(NH) 3070.75(-OH) 1708.02(-C=O s) 1530.57(Ar) **$^1$HNMR**; 2.37(3Hs. J6.75. Ar-$CH_3$),3.56-3.54(2Hs.J.10.34. $CH_2$), 4.33(-NH.J.0.81.NH) 7.36(1Hd. J4.53.Ar-H) 7.38(1Hd.Ar-H) 7.70(1Hd.

J4.35.Ar-H), 7.96(1Hd. J.2.28.Ar-H) 12.56(-OH-dwarf peak), **$^{13}$C NMR;** 170.67$_{C1}$, 143.08$_{C2}$, 129.96$_{C3}$, 72.62$_{C4}$, 126.99$_{C5}$, 138.26$_{C6}$, 21.41$_{C7}$, 173.55$_{C1'}$, 44.23$_{C2'}$.

**2-[4-methylphenylsulphonamido]-4-methylpentanoic acid [3c]**

The amino acid is leucine **[1c]**. The molecular formula is $C_{11}H_{13}NO_4S$, Weight is 255.29, Theoretical yield is 2.82g, experimental, 1.98g (70.21%), $R_f$ 0.83 and mp. 78-79$^0$C. **FT-IR(KBr)(cm$^{-1}$);** 1155.4(S=O), 3361.07( -NH), 3070.78( –OH-),1707.06( –C=O) 1529.6( –$CH_3$). **$^1$H NMR;** 0.67-0.69(3Hd.J2.89-$CH_3$), 0.72-0.74(3Hd. J.3.36-$CH_3$), 1.33-1.38(3Hs. Ar-$CH_3$), 1.44(1Hm.CH), 1.62(2Ht.$CH_2$) , 3.62-3.70(1H. J. 1.8. CH), 4.36(-NH), 7.65-7.67(1Hd. J.2.04 Ar-H), 8.03(-OH-J.1.00), 7.32-7.35(1Hd. J.2.02 Ar-H). **$^{13}$C NMR;**173.57$_{C1}$, 142.88$_{C2}$, 129.77$_{C3}$, 72.62$_{C4}$, 126.97$_{C5}$, 138.78$_{C6}$, 23.00$_{C7}$, 172.71$_{C1'}$, 54.50$_{C2'}$, 24.30$_{C3'}$, 41.42$_{C4'}$, 21.46$_{C5'}$, 21.38$_{C6'}$.

**2-[4-methylphenylsulphonamido]-3-phenylpropanoic acid [3d]**

The amino acid is phenylalanine **[1d]**. The molecular formula is $C_{16}H_{17}NO_4S$, Weight is 319.38, Theoretical yield is 3.99g, experimental 3.06g (76.69%), $R_f$ 0.57 and mp. 103-104$^0$C. **FT-IR(KBr)(cm$^{-1}$);** 1161.1(S=O), 3320.57(-NH), 1702.24(C=O), 3421.83(-OH), 1415.8(-$CH_3$), 1546.96(Ar). **$^1$H NMR;** 2.31(1Hs.J.3.16. Ar-$CH_3$), 2.72-2.99(Ph-H.J.1.10), 4.32(NH.J.0.70), 5.73(2Hd. J.1.17 –$CH_2$), 7.11-7.23(1Hd. J. 7.69 Ar-H) 7.29(1Hd Ar-H), 7.48-7.57[(1Hdx2) J. 2.24.Ar-H], 7.98(-OH-dwarf peak. J.1.00). **$^{13}$C NMR;**172 .93$_{C1}$, 138.53$_{C2}$, 129.74$_{C3}$, 58.04$_{C4}$, 129.68$_{C5}$, 137.36$_{C6}$, 21.37$_{C7}$, 174.30$_{C1'}$, 142.78$_{C2'}$, 38.42$_{C3'}$, 72.60$_{C4'}$, 126.78, 126.83, and 128.54$_{Ph}$.

**2-[4-methylphenylsulphonamido]-3-methylbutanoic acid [3e]**

The amino acid is valine **[1e]**. The molecular formula is $C_{10}H_{13}NO_4S$, Weight is 271.33, Theoretical yield is 3.39g, experimental 3.32g (98%), $R_f$ 0.74 and mp. 125-126$^0$C. **FT-IR (KBr) (cm$^{-1}$);** 1150.58(S=O), 3489.7(-NH), 1704.17(C=O), 3418.94(-OH), 1430.26(-$CH_3$), 1543.1(Ar). **$^1$H NMR;** 0.77-0.83 (3Hd. J.5.91.-$CH_3$X2), 1.89-1.93(3Hs. J. 1.05 Ar-H), 2.36(1Hm.J.2.30. - CH), 3.52(1Hd.J.2.13. –CH), 4.34(-NH), 7.88-7.91(-OH-), 7.65-7.67(1Hd.J.1.97. Ar-H), 7.32-7.35(1Hd. J.1.94. Ar-H). **$^{13}$C NMR;**172.64$_{C1}$, 142.82$_{C2}$, 129.74$_{C3}$, 72.61$_{C4}$, 127.02$_{C5}$, 138.81$_{C6}$, 21.40$_{C7}$, 173.55$_{C1'}$, 61.66$_{C2'}$, 30.85$_{C3'}$, 19.43$_{C4'}$, 19.31$_{C5'}$.

**2.2 Preparation of the inoculums**

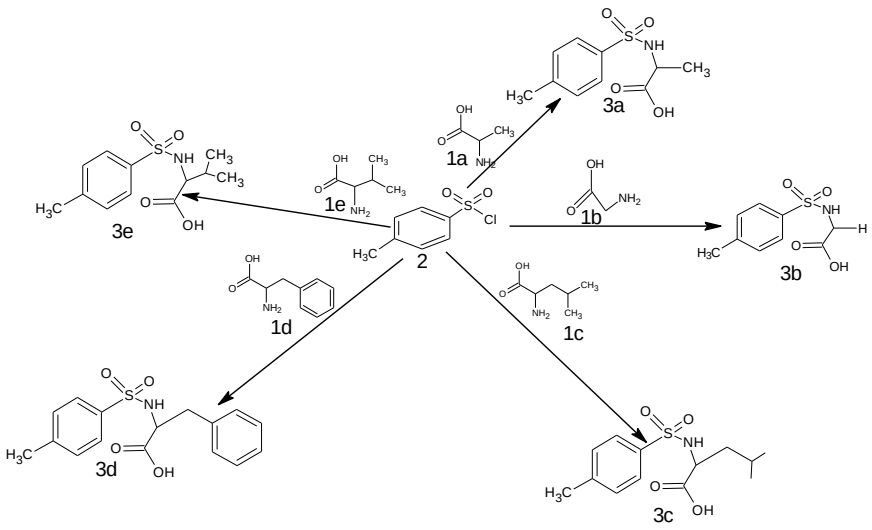
The standard clinical isolated organisms of *Staphylococcus aurous, Pseudomonas, Streptococcus, klebsiella, Escherichia coli a*nd *Proteus* were obtained from FMC Owerri and the analysis was carried at Department of Medical Science Laboratory Imo state University. The strains of the organisms were propagated on nutrient agar plates and maintained at 4$^0$C. The isolates were sub-cultured in nutrient broth at 37$^0$C for 8h prior to antibacterial testing.

**Antibacterial sensitivity testing of compounds**

Agar well diffusion technique as described by Adeniyi *et* al [12] was used to determine the antibacterial activity of the synthesised compounds. Sensitivity test agar plates were inoculated with 0.1ml of an overnight culture of each bacteria strain (equivalent to $10^8$ CFU/ml$^{-1}$). The inoculated agar plates were allowed to dry and were appropriately labelled. Using a plastic cork borer of 6mm in diameter uniformed wells was bored in the inoculated nutrient agar. With a micropipette, 200µl of 10mg/ml of each test compound solution was delivered into each well. Ciprofloxacin which is used as the positive standard was also tested and the plates were left on the bench for 30minutes to allow the compound to diffuse into the agar. Thereafter, the plates were incubated at 37˚C for 24h. After incubation, the plates were observed for inhibition zones around the wells. The diameters of the zones were measured with metre rule to the nearest whole millimetre.

## III. Results And Discussion

The synthesis of Para-toluene sulphonamide derivatives of amino acids was obtained by reacting P-Toluene sulphonylchloride with primary amine functionalities of five amino acids [1a-1e] in alkaline medium at the temperature below 0$^0$C to produce P-toluene sulphonamides [3a-3e] (scheme 1).




**Scheme 1:** Synthesis of Para-toluene sulphonamides [3a-3e].

The carboxylic end (-COOH) of the amino acid was converted to the sodium salt of the acid through electrophilic substitution of the $H^+$ with $Na^+$ released from the base ($Na_2CO_3$). The formation of the sodium salt helped to protect the (-COOH) of the amino acids and enhanced the solubility of the amino acids in aqueous medium.

The nucleophilic attack of the electrophilic sulphur 0f the P-toluene sulphonyl chloride [2] by the amino group of the amino acids [1a-1e] form ammonium ion. The abstraction of the ammonium proton by the leaving group chloride ion led to the amide which underwent acidification with 20Molar HCl to afford the expected Para-toluene sulphonamide [3a-3e]

Structures of the synthesised compound were established by IR, NMR ($^1H$, $^{13}C$) and elemental analysis. The assignments C1-C7 are for carbons of Para-toluene sulphonyl carbons while C1'-C6' are for the carbons of amino acids (alkanoic acids). All the synthesised compounds were white crystalline solids and their melting points ranges from $78^0C$-$126^0C$. The FT-IR ($CM^{-1}$) showed –SO- signals at the range of 1140.83-1162.15; -NH- signals at 3320.57-3489.7; and -CO- signals at 1702.24-1708.02. The NMR spectral ($^1H$) showed –OH-chemical shift at δ7.88- δ12.56 with **[3b]** having the highest value of δ12.56 because of the lower number of protons at the alpha carbon of the carboxyl carbon and this reduced the pull of electron from –OH-. The carbon-13 ($^{13}C$) chemical shift at δ21.27- δ23.00 indicated the saturated methyl carbon of the Para-toluene moity of the synthesised compounds while the carbonyl carbon C1' were observed at chemical shift δ172.71- δ178.70. The combination of IR, NMR and the elemental analytical data confirmed the synthesis of the compounds **[3a-3e]**.
The anti bacterial screening carried out with 200µl of 10mg/ml of each synthesised compound showed active inhibition properties on the growth of *Staphylococcus aurous*, *Pseudomonas aeruginosa*, *Streptococcus*, *klebsiella pneumonia*, *Escherichia coli* and *Proteus mirabilis*. (table. 1)

**Table. 1:**Results of Anti-bacterial Susceptibility of P-toluene sulphonamides with 200µl of 10mg/ml of each compound in [mm]

| COMPD | STAPH | PROTEUS | E-COLI | PSEUDO | KLEB | STREP |
|---|---|---|---|---|---|---|
| 3a | 17 | 16 | 20 | 18 | 14 | 17 |
| 3b | 16 | 15 | 18 | 19 | 16 | 17 |
| 3c | 16 | 17 | 19 | 19 | 14 | 17 |
| 3d | 18 | 19 | 20 | 19 | 17 | 20 |
| 3e | 16 | 25 | 16 | 19 | 15 | 19 |
| CPX | 24 | 22 | 26 | 22 | 28 | 22 |

Cpx= Ciprofloxacin (standard drug).

## IV. Conclusion

Para-toluene sulphonamide derivatives of amino acids **(3a-3e)** have been successfully synthesised by the nucleophilic attack of the amino group of the amino acids [1a-1e] on the electrophilic sulphur 0f the P-toluene sulphonyl chloride [2]. The synthesised compounds exhibited potent antibiotics properties since they showed zone of inhibition with 200µl of 10mg/ml of each tested organism.

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