



Research Article

Synthesis and Spectral Study of N,N-diethyl-2-methyl-1-tosylpyrrolidine-2-carboxamide and Functionalized Sulfonamide Scaffolds

¹Olayinka O. Ajani, ²Joseph D. Udonne, ¹Cyril O. Ehi-Eromosele, ¹Joseph A.O. Olugbuyiro, ¹Damilola V. Aderohunmu, ¹Christiana O. Ajanaku and ¹Oluwatosin Y. Audu

¹Department of Chemistry, Covenant University, CST, Canaanland, Km 10 Idiroko Road, P.M.B. 1023, Ota, Ogun State, Nigeria

²Department of Chemical and Polymer Engineering, Lagos State University, Lagos State, Nigeria

Abstract

Background and Objective: Sulfonamides are known to represent a class of medicinally important compounds and chemical intermediates, which are extensively used in drug development. The aim of this present study is to synthesize a series of arylsulfonamide-based dialkylated amide motifs. **Materials and Methods:** In this study, the design and development of arylsulfonamide pharmacophore bearing N,N-diethyl substituted amide moieties 2a-k was achieved in improved yields using non-conventional amidation of p-tolylsulfonamide precursors 1a-k. The structures of the compounds were substantiated based on the results of elemental analysis and spectroscopic data namely, FT-IR, ¹H-NMR, ¹³C-NMR and mass spectra. **Results:** The series of targeted compounds were synthesized in good to excellent yields and subsequently purified by column chromatography where necessary. **Conclusion:** The synthesis of arylsulfonamide-based dialkylated amide motifs was successfully achieved. These compounds may serve as versatile intermediates that pave ways toward achieving diverse bioactive heterocyclic compounds for future drug discovery and development.

Key words: Tosylation, amidation, carboxamide, sulfonamide, spectroscopy

Received:

Accepted:

Published:

Citation: Olayinka O. Ajani, Joseph D. Udonne, Cyril O. Ehi-Eromosele, Joseph A.O. Olugbuyiro, Damilola V. Aderohunmu, Christiana O. Ajanaku and Oluwatosin Y. Audu, 2016. Synthesis and spectral study of N,N-diethyl-2-methyl-1-tosylpyrrolidine-2-carboxamide and functionalized sulfonamide scaffolds. *Curr. Res. Chem.*, CC: CC-CC.

Corresponding Author: Olayinka O. Ajani, Department of Chemistry, Covenant University, CST, Canaanland, Km 10 Idiroko Road, P.M.B. 1023, Ota, Ogun State, Nigeria Tel: +2348061670254

Copyright: © 2016 Olayinka O. Ajani *et al.* This is an open access article distributed under the terms of the creative commons attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

In primary care medicine, sulfonamides are widely used in various conditions including gastrointestinal¹ and urinary tract infections². In fact, sulfonamide which is the organic framework of main focus in this present study belongs to the family of sulfur-containing compounds with -SO₂NH- functionality which are earlier referred to as the sulfa drugs³. The characterization of sulfonamides as chemotherapeutics is more than half a century old⁴. Since, then, the sulfonamide group has been found as a key structural motif shared by a large number of bioactive compounds⁵⁻⁷. In view of this, consistent exploration of sulfonamide chemistry has led to the development of highly versatile probes with a broad range of applications, some of, which include activatable photosensitizers⁸, chemosensors with selective fluorescence enhancement among others⁹. Sulfonamide containing moieties are reported to be self-assembled into robust two dimensional molecular layers¹⁰ as well as being valuable building block for higher order superstructures¹¹.

Furthermore, due to high industrial relevance and wide applications, a variety of protocols were available for the synthesis of sulfonamide. Among the various methods reported, it is obvious that the most convenient and efficient ways involved the reaction of sulfonyl chloride derivatives with nucleophilic amino containing templates, such as 1-naphthylmethyl amine¹², substituted aniline¹³, piperidine¹⁴, ethanamine¹⁵, benzo[d]thiazol-2-amine¹⁶, dimethyl 2-aminopentanedioate¹⁷, 8-aminoquinoline¹⁸, cyclohexanamine¹⁹, diprotected glutamic acid²⁰, pyrrole²¹ and morpholine²² to afford the respective sulfonamide products. Many derivatives of sulfonamide have been explored as important starting materials and reactive intermediates in various organic syntheses²³⁻²⁵. This authenticates their well-established utility in the synthesis of pyrrolidines²⁶, isothiourea²⁷, secondary amine²⁸, superacid mediated reaction²⁹, enantioselective reduction of α -ketoester³⁰ and monoalkylation of amino group³¹. It has also proved to be vital precursor in the total synthesis of some natural product, such as (-)-cylindricine³², lepadiformine³³, fasicularin³⁴ and natural-product-like molecules³⁵.

In a similar manner, amide formation is a fundamental reaction of great interest in organic chemistry³⁶. The development of efficient methods for the synthesis of amides remains an excellent idea because of their importance in chemistry and biology, with a wide range of industrial and pharmaceutical applications and as valuable intermediates in organic synthesis³⁷. Hence, it is conceivable to design the synthetic route in this present study in such a way to have

amide functionality being incorporated within the framework of the synthesized sulfonamides. This might probably lead to discovery of compounds with increase biological activity for future drug design and also help in the comparative study of pharmacological properties of the ordinary sulfonamide to that of amide-bearing sulfonamide derivatives.

MATERIALS AND METHODS

General condition: The melting points were determined on XT-4 Digital Binocular Microscope melting point apparatus and were uncorrected. The IR spectra were run on Varian Excalibur HE 3100 FT-IR Spectrometer while the Mass Spectra were obtained using Waters GCT Premier Spectrometer. The ¹H-NMR spectra were recorded in either CDCl₃ or DMSO-d₆ on NMR Bruker DPX400 spectrometer operating at 400 MHz. Tetramethyl silane (TMS) was used as internal standard with the deuterium signal of the solvent as the lock and chemical shifts δ recorded in ppm. The elemental analysis (C, H and N) of the compounds were performed using Flash EA 1112 Elemental Analyzer. The pH was monitored using Portable pH Meter Model PHB4. All drying was conducted at reduced pressure with DHG-9023A Vacuum Oven. In addition, column chromatographic purifications were carried out on the products using CHCl₃/CH₃OH (9:1) solvent system and Merck silica gel F (Mesh 200-300). Organic solutions were dried over anhydrous Na₂SO₄ and concentrated with a RE-2000B Buchi Rotary Evaporator. Commercially available materials were used without further purification, while other reagents were used directly after ascertaining the purity condition.

General procedure for p-toluenesulfonamide (1a-k): To a solution of amino acid (12.5 mmol) in water (15 mL) was added Na₂CO₃ (2.785 g, 26.25 mmol) at 0°C and p-toluenesulfonyl chloride, p-TsCl (2.86 g, 15 mmol) in 3 portions over a period of 1 h. The slurry was then warmed to room temperature and allowed to stir for 48 h. Upon completion of the reaction, which was TLC monitored using CHCl₃/CH₃OH solvent system (9:1), the reaction mixture was acidified with 20% concentrated aqueous HCl solution to pH 2, after which crystallization occurred and the product was obtained via suction filtration. The filtered crude product was washed with pH 2.2 buffer and dried in a vacuum oven at 60°C for 12 h to afford p-toluenesulfonamides (1a-k).

1-(4-methylphenylsulfonamido) pyrrolidine-2-carboxylic acid (1a): The IR: 3217 (OH), 2939 (CH aliphatic), 2860 (CH arom.), 1734 (C=O of COOH), 1601 (C=C arom.), 1152, 1094 (SO₂ two bands), 662 (Ar-H). ¹H-NMR (400 MHz,

DMSO- d_6): 7.72-7.70 (d, $J = 8.0$, 2H, Ar-H), 7.43-7.41 (d, $J = 8.0$, 2H, Ar-H), 4.08-4.05 (m, 1H), 3.36-3.30 (m, 1H), 3.16-3.10 (m, 1H), 2.39 (s, 3H, CH_3), 1.86-1.76 (m, 3H), 1.58-1.49 (m, 1H). ^{13}C -NMR (400 MHz, DMSO- d_6): 173.2 (C=O), 143.5, 134.7, 129.9, 127.2, 67.1, 60.5, 48.5, 30.5, 25.2, 24.3 and 21.1. The EI-MS (% rel.): 269.1 (M^+ , 11), 179.1 (21), 178.1 (100), 176.1 (34), 122.0 (49) and 105 (32).

1-(4-methylphenylsulfonamido) piperidine-2-carboxylic acid (1b): The 1H -NMR (400 MHz, $CDCl_3$): 7.70-7.68 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.28-7.26 (d, $J = 8.0$ Hz, 2H, Ar-H), 4.74-4.73 (m, 1H), 3.72-3.69 (d, $J = 12.0$ Hz, 1H), 3.23-3.17 (t, $J = 12.0$ Hz, 1H), 2.41 (s, 3H, CH_3 -Ar), 2.18-2.15 (m, 1H), 1.67-1.55 (m, 3H), 1.45-1.31 (m, 2H). ^{13}C -NMR (400 MHz, DMSO- d_6): 171.6 (C=O), 142.9, 137.4, 129.6 ($2 \times CH$ arom.), 126.8 ($2 \times CH$ arom.), 54.6, 42.1, 27.0, 23.9, 21.0 (CH_3), 19.7 (CH_2). EI-MS (% rel.): 239.1 (M^+ - CO_2 , 10), 238.1 (74), 220.1 (37), 191.1 (28), 91.1 (100).

2-(4-methylphenylsulfonamido)acetic acid (1c): The IR: 3279 (N-H), 3102 (OH), 2980 (CH aliphatic), 1726 (C=O of COOH), 1595 (C=C aromatic), 1234, 1161 (SO_2 two bands), 669 (Ar-H). 1H -NMR (400 MHz, DMSO- d_6): 12.63 (s-br, 1H), 7.95-7.92 (t, $J = 6.0$ Hz, 1H), 7.68-7.66 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.38-7.36 (d, $J = 8.0$ Hz, 2H, Ar-H), 3.55-3.53 (d, $J = 6.0$ Hz, 2H), 2.37 (s, 3H). EI-MS (% rel.): 238.1 (41), 184.0 (55), 155.0 (100), 91.1 (65), 65.0 (63), 44.0 (39).

2-(4-methylphenylsulfonamido)propanoic acid (1d): The IR: 3277 (N-H), 3084 (OH), 2934 (CH aliphatic), 1715 (C=O of COOH), 1649 (C=C aromatic), 1233 1150 (SO_2 two bands), 677 (Ar-H). 1H -NMR (400 MHz, DMSO- d_6): 8.05-8.03 (d, $J = 8.3$ Hz, 1H), 7.67-7.65 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.37-7.35 (d, $J = 8.0$ Hz, 2H, Ar-H), 3.74-3.71 (m, 1H), 2.37 (s, 3H), 1.13-1.12 (d, $J = 7.2$ Hz, 3H). EI-MS (% rel.): 199.1 (M^+ - CO_2 , 12), 198.0 (89), 156.0 (21), 155.0 (98), 91.1 (100), 65.0 (47), 44.1 (27).

3-mercapto-2-(4-methylphenylsulfonamido)propanoic acid (1e): The IR: 3445 (N-H), 3003 (OH), 2907 (CH aliphatic), 1736 (C=O of COOH), 1596 (C=C aromatic), 1221, 1152 (SO_2 two bands), 679 (Ar-H). 1H -NMR (400 MHz, DMSO- d_6): 8.59-8.53 (s-br, 1H), 7.81-7.79 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.28-7.26 (d, $J = 8.0$ Hz, 2H, Ar-H), 5.83-5.81 (d, $J = 8.4$ Hz, 1H), 3.81-3.78 (m, 1H), 3.10-3.08 (d, $J = 7.63$ Hz, 2H), 2.37 (s, 3H).

2-(4-methylphenylsulfonamido)-4-(methylthio) butanoic acid (1f): The IR: 3566 (N-H), 2982 (CH aliphatic), 2874 (CH aromatic), 1740 (C=O), CH_3 -S (1653), 1609 (C=C), 1148,

1109 (SO_2 two bands), 671 (Ar-H). 1H -NMR (400 MHz, $CDCl_3$): 7.75-7.73 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.29-7.27 (d, $J = 8.0$ Hz, 2H, Ar-H), 5.75 (s-br, 1H), 4.07 (s-br, 1H), 3.25 (s-br, 2H), 2.50-2.48 (m, 1H), 2.40 (s, 3H), 1.99 (s, 3H), 1.95-1.89 (m, 1H).

3-methyl-2-(4-methylphenylsulfonamido) butanoic acid (1g): The IR: 3289 (N-H), 2967 (CH aliphatic), 1711 (C=O of COOH), 1595 (C=C aromatic), 1335, 1163 (SO_2 two bands), 687 (Ar-H). 1H -NMR (400 MHz, $CDCl_3$): 7.73-7.71 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.29-7.27 (d, $J = 8.0$ Hz, 2H, Ar-H), 5.07-5.04 (d, $J = 9.9$ Hz, 1H), 3.82-3.78 (dd, $J_1 = 4.6$ Hz, $J_2 = 9.9$ Hz, 1H), 2.43 (s, 3H), 2.11-2.08 (m, 1H), 0.97-0.96 (d, $J = 6.8$ Hz, 3H), 0.88-0.86 (d, $J = 6.8$ Hz, 3H). EI-MS (% rel.): 270.1 (M^+ -H, 23), 227.1 (11), 226.1 (100), 155.0 (98), 92.1 (33), 91.1 (92), 65.0 (48).

3-hydroxy-2-(4-methylphenylsulfonamido) butanoic acid (1h): The IR: 3501 (OH free), 3435 (N-H), 3360 (OH of COOH), 3262 (N-H), 2976 (CH aliphatic), 1697 (C=O), 1595 (C=C aromatic), 1273, 1167 (SO_2 two bands), 673 (Ar-H). The 1H -NMR (400 MHz, DMSO- d_6): 7.68-7.66 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.54-7.50 (d, $J = 9.2$, 1H), 7.34-7.32 (d, $J = 8.0$ Hz, 2H, Ar-H), 3.98-3.92 (m, 1H), 3.64-3.61 (dd, $J_1 = 3.6$ Hz, $J_2 = 9.2$ Hz, 1H), 2.36 (s, 3H), 2.08 (s, 1H), 1.01-0.99 (d, $J = 6.36$ Hz, 3H).

5-amino-2-(4-methylphenylsulfonamido)-5-oxopentanoic acid (1i): The IR: 3456 (N-H), 3331 (OH of COOH), 3246 (N-H), 2955 (CH aliphatic), 1678 (C=O), 1640 (C=O), 1570 (C=C aromatic), 1167, 1094 (SO_2 two bands), 685 (Ar-H). 1H -NMR (400 MHz, DMSO- d_6): 8.06-8.04 (d, $J = 8.8$ Hz, 1H), 7.65-7.63 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.36-7.34 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.24 (s-br, 1H), 6.74 (s-br, 1H), 3.69-3.65 (ddd, $J_1 = 3.08$ Hz, $J_2 = 5.52$ Hz, $J_3 = 8.8$ Hz, 1H), 2.37 (s, 3H, CH_3 -Ar), 2.08-2.06 (t, $J = 7.68$ Hz, 2H), 1.85-1.79 (m, 1H), 1.67-1.61 (m, 1H). EI-MS: m/z (% rel.): 246.0 (97), 238.1 (16), 171.0 (49), 156.0 (84), 139.0 (52), 123.0 (100), 92.1 (38), 77.0 (41), 44.0 (32).

2-(4-methylphenylsulfonamido)-3-phenylpropanoic acid (1j): The IR: 3350 (N-H), 3188 (OH), 2961 (CH aliphatic), 1736 (C=O of COOH), 1350, 1171, 1092 (SO_2 two bands), 675 (Ar-H). 1H -NMR (400 MHz, $CDCl_3$): 7.61-7.59 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.24-7.21 (m, 5H, Ar-H), 7.10-7.08 (m, 2H, Ar-H), 5.16-5.13 (d, $J = 8.64$ Hz, 1H), 4.21-4.17 (ddd, $J_1 = 5.6$ Hz, $J_2 = 6.4$ Hz, $J_3 = 8.64$ Hz, 1H), 3.12-3.08 (dd, $J_1 = 5.6$ Hz, $J_2 = 20.0$ Hz, 1H), 3.03-2.98 (dd, $J_1 = 6.4$ Hz, $J_2 = 20.0$ Hz, 1H), 2.40 (s, 3H). The ^{13}C -NMR (100 MHz, $CDCl_3$): 174.9 (C=O), 143.9, 136.6, 134.9, 129.8 ($2 \times CH$ arom.), 129.6 ($2 \times CH$ arom.), 128.8 ($2 \times CH$ arom.), 127.4 ($2 \times CH$ arom.), 127.2, 56.5, 39.0 (CH_2), 21.7 (CH_3).

2-(4-methylphenylsulfonamido)-3-(4-(tosyloxy)phenyl) propanoic acid (1k):

The IR: 3561 (N-H), 3339 (OH of COOH), 2924 (CH aliphatic), 1717 (C=O), 1559 (C=C arom.), 1150, 1092 (SO₂ two bands), 669 (Ar-H). The ¹H-NMR (400 MHz, CDCl₃): 7.69-7.67 (d, J = 8.26 Hz, 2H, Ar-H), 7.59-7.57 (d, J = 8.26 Hz, 2H, Ar-H), 7.32-7.30 (d, J = 8.0 Hz, 2H, Ar-H), 7.24-7.22 (d, J = 8.0 Hz, 2H, Ar-H), 7.03-7.01 (d, J = 8.4 Hz, 2H, Ar-H), 6.85-6.83 (d, J = 8.4 Hz, 2H, Ar-H), 5.14-5.12 (d, J = 8.48 Hz, 1H), 4.17-4.12 (q, J = 6.8 Hz, 1H), 3.11-3.06 (dd, J₁ = 5.2 Hz, J₂ = 20.0 Hz, 1H), 2.97-2.92 (dd, J₁ = 6.8 Hz, J₂ = 20.0 Hz, 1H), 2.45 (s, 3H), 2.41 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃): 173.7 (C=O), 149.1, 145.8, 144.1, 136.4, 134.1, 132.2 (six benzylic arom. C), 130.9 (2×CH arom.), 130.0 (2×CH arom.), 129.9 (2×CH arom.), 128.6 (2×CH arom.), 127.2 (2×CH arom.), 122.6 (2×CH arom.), 56.4 (CH), 38.3 (benzylic CH₂), 21.9 (CH₃ linked to OSO₂-Ar), 21.7 (CH₃ linked to SO₂-Ar). EI-MS: m/z (% rel.): 443.1 (23), 171.0 (35), 156.0 (58), 155.0 (90), 134.1 (90), 92.1 (64), 65.0 (100).

General procedure for synthesis of amidated sulfonamides

(2a-k): A three-necked 250 mL flask equipped with magnetic stirring bar was charged with appropriate p-toluene sulfonamide 1a-k (2.96 mmol) and dichloromethane, DCM (10 mL). The flask was closed, cooled to 0°C and nitrogen was bubbled into it continuously. Oxalyl chloride (0.34 mL, 3.85 mmol, 1.3 equiv.) was cautiously added via dropping pipette to maintain the temperature below 10°C followed by the addition of 2 drops of DMF. The resulting mixture was stirred at room temperature until the conversion to acid chloride was completed (i.e., for about 1.5 h) and then concentrated to dryness with rotary evaporator (23°C, 40 mmHg). To the resulting crude acid chloride was added DCM (20 mL) and the solution was concentrated again. In a separate 250 mL three-necked round bottom flask, equipped with a magnetic stirring bar, a N₂ inlet, a rubber septum, 125 mL pressure equalizing addition funnel and a temperature probe was charged DCM (10 mL), triethyl amine (0.62 mL, 4.44 mmol, 1.5 equiv.) and diethyl amine (0.4 mL, 3.85 mmol, 1.3 equiv.) and the mixture was cooled to -10°C.

The crude acid chloride was dissolved in DCM (10 mL) and this solution was transferred to the addition funnel. The acid chloride was then added drop-wisely to the stirred diethyl amine solution at such a rate that the internal temperature was maintained below 10°C. Upon completion of the addition of the acid chloride solution (ca 30 min), the mixture was stirred at -10 to 0°C for 1 h and at room temperature for 1 h. The mixture was then diluted with 2N HCl (6 mL) and was transferred into a 250 mL separatory funnel and the layers separated. The organic layer was washed with brine

(6 mL) and was then concentrated under reduced pressure (23°C, 40 mmHg), diluted with methanol (6 mL) and re-concentrated to give a crude solid. The solid was slurried in methanol (7.5 mL) and water (15 mL) was added drop-wisely with continuous stirring for 10 min. The slurry was stirred at room temperature for 1 h and allowed to crystallize. It was filtered by suction and dried under vacuum/N₂ sweep for 8 h to afford required N,N-diethyl substituted p-tolylsulfonamides (2a-k).

N,N-diethyl-1-tosylpyrrolidine-2-carboxamide (2a): The IR: 2976 (CH aromatic), 2872 (CH aliphatic), 1678 (C=O of amide), 1609 (C=C), 1155, 1107 (SO₂ two bands), 669 (Ar-H). ¹H-NMR (400 MHz, CDCl₃): 7.77-7.75 (d, J = 8.0 Hz, 2H, Ar-H), 7.28-7.26 (d, J = 8.0 Hz, 2H, Ar-H), 4.77-4.74 (dd, J₁ = 3.6 Hz, J₂ = 11.2 Hz, 1H), 3.49-3.41 (m, 2H), 3.40-3.38 (m, 1H), 3.34-3.29 (m, 2H), 2.40 (s, 3H), 2.09-2.03 (m, 2H), 1.89-1.81 (m, 2H), 1.27-1.24 (t, J = 7.12 Hz, 3H), 1.10-1.06 (t, J = 7.10 Hz, 3H), 0.89-0.87 (m, 1H). EI-MS: m/z (% rel.): 225.0 (62), 224.0 (100), 169.1 (89), 155.0 (93), 100.1 (17), 91.0 (82), 72.0 (45), 65.0 (42).

N,N-diethyl-2-methyl-1-tosylpyrrolidine-2-carboxamide

(2a₂): The IR: 2949 (CH arom.), 2860 (CH aliphatic), 1713 (C=O of amide), 1601 (C=C), 1159, 1115 (SO₂ two bands), 654 (Ar-H). ¹H-NMR (400 MHz, CDCl₃): 7.76-7.73 (dd, J₁ = 6.0 Hz, J₂ = 12.0 Hz, 2H, Ar-H), 7.33-7.31 (d, J = 8.0 Hz, 1H, Ar-H), 7.28-7.26 (d, J = 6.88 Hz, 1H, Ar-H), 4.73-4.70 (dd, J₁ = 4.0 Hz, J₂ = 11.88 Hz, 1H), 4.26-4.24 (dd, J₁ = 3.6 Hz, J₂ = 11.88 Hz, 1H), 3.48-3.40 (d, J = 7.2 Hz, 2H), 3.34-3.23 (d, J = 7.12 Hz, 2H), 2.42 (s, 3H), 2.39 (s, 3H), 2.13-2.03 (m, 2H), 1.96-1.71 (m, 2H), 1.26-1.23 (t, J = 7.2 Hz, 3H), 1.09-1.05 (t, J = 7.12 Hz, 3H).

N,N-diethyl-1-tosylpiperidine-2-carboxamide (2b):

The ¹H-NMR (400 MHz, CDCl₃): 7.58-7.56 (d, J = 8.0 Hz, 2H, Ar-H), 7.21-7.19 (d, J = 8.0 Hz, 2H, Ar-H), 4.86-4.85 (m, 1H), 3.73-3.70 (q, J = 7.2 Hz, 2H), 3.31-3.26 (q, J = 7.08 Hz, 2H), 3.17-3.14 (m, 1H), 3.07-3.04 (m, 1H), 2.36 (s, 3H), 1.75-1.62 (m, 3H), 1.54-1.42 (m, 3H), 1.26-1.23 (t, J = 7.2 Hz, 3H), 0.96-0.93 (t, J = 7.08 Hz, 3H).

N,N-diethyl-2-(4-methylphenylsulfonamido) acetamide

(2c): The IR: 3034 (CH arom.), 2946 (CH aliphatic), 1707 (C=O of amide), 1601 (C=C), 1191, 1145 (SO₂ two bands), 694 (Ar-H). ¹H-NMR (400 MHz, CDCl₃): 7.75-7.73 (d, J = 8.0 Hz, 2H, Ar-H), 7.29-7.27 (d, J = 8.0 Hz, 2H, Ar-H), 5.80 (s-br, 1H), 3.73-3.72 (d, J = 4.1 Hz, 2H), 3.30-3.25 (q, J = 7.14 Hz, 2H), 3.17-3.11 (q, J = 7.18 Hz, 2H), 2.40 (s, 3H), 1.12-1.08 (t, J = 7.18 Hz, 3H), 1.02-0.99 (t, J = 7.14 Hz, 3H).

N,N-diethyl-2-(4-methylphenylsulfonamido)propanamide

(2d): The IR: 3279 (NH), 3107 (CH aromatic), 1711 (C=O of amide), 1620 (C=C), 1152, 1090 (SO₂ two bands), 677 (Ar-H). The ¹H-NMR (400 MHz, CDCl₃): 7.74-7.66 (m, 2H, Ar-H), 7.27-7.22 (m, 2H, Ar-H), 5.46-5.44 (d, J = 8.48 Hz, 1H), 4.20-4.16 (m, 1H), 3.97-3.90 (q, J = 7.12 Hz, 2H), 3.15-3.10 (m, 1H), 2.39 (s, 3H), 1.39-1.37 (d, J = 7.16 Hz, 3H), 1.17-1.02 (t, J = 7.12 Hz, 3H).

N,N-diethyl-3-methyl-2-(4-methylphenylsulfonamido)

butanamide (2g): The IR: 3260 (NH), 2974 (CH arom.), 1668 (C=O of amide), 1167, 1090 (SO₂ two bands), 689 (Ar-H). The ¹H-NMR (400 MHz, CDCl₃): 7.68-7.66 (d, J = 8.0 Hz, 2H, Ar-H), 7.23-7.21 (d, J = 8.0 Hz, 2H Ar-H), 5.78-5.75 (d, J = 9.24 Hz, 1H), 3.81-3.78 (dd, J₁ = 4.22 Hz, J₂ = 9.24 Hz, 1H), 3.09-3.00 (m, 4H), 2.36 (s, 3H), 1.82-1.77 (m, 1H), 1.03-1.01 (d, J = 6.8 Hz, 3H), 0.92-0.88 (t, J = 7.2 Hz, 3H), 0.84-0.82 (d, J = 6.0 Hz, 3H), 0.84-0.81 (t, J = 6.48 Hz, 3H).

N,N-diethyl-2-(4-methylphenylsulfonamido)-3-phenylpropanamide (2j):

The IR: 3306 (NH), 2947 (CH aliphatic), 1710 (C=O of amide), 1601 (C=C), 1213, 1171 (SO₂ two bands), 685 (Ar-H). ¹H-NMR (400 MHz, CDCl₃): 7.63-7.61 (d, J = 8.0 Hz, 2H, Ar-H), 7.21-7.18 (m, 5H, Ar-H), 7.12-7.10 (d, J = 8.0 Hz, 2H, Ar-H), 5.88-5.86 (d, J = 9.48 Hz, 1H), 4.31-4.25 (m, 1H), 3.21-3.15 (m, 1H), 2.97-2.96 (m, 1H), 2.92-2.86 (m, 2H), 2.79-2.74 (q, J = 7.2 Hz, 2H), 2.37 (s, 3H), 0.88-0.84 (t, J = 7.14 Hz, 3H), 0.74-0.71 (t, J = 7.2 Hz, 3H).

Synthesis of N,N-diethyl-4-methylbenzenesulfonamide

(2d₂): To a solution of diethyl amine (0.16 mL, 1.5 mmol) in DCM (5 mL) was added sodium hydroxide (0.16 g, 4 mmol) in water (10 mL). The mixture was stirred and maintained at a temperature of -10°C, while a solution of acid chloride of 1d (0.4 g, 1.5 mmol) in DCM (5 mL) was drop-wisely added over a period of 1 h. It was warmed up to 10°C, stirred there for 1 h and the organic layer was separated. The aqueous layer was extracted with two 15 mL portion of DCM. The organic layer was combined, washed with 5 mL of 5% hydrochloric acid, two 5 mL portion of sodium bicarbonate and 5 mL of water. The organic layer was dried over anhydrous sodium sulfate and DCM was removed through rotary evaporator to afford an oily substance (2d₂). The IR: 2980 (CH aliphatic), 2876 (CH aromatic), 1632 (C=C), 1148, 1112 (SO₂ two bands), 670 (Ar-H). The ¹H-NMR (400 MHz, CDCl₃): 7.70-7.68 (d, J = 8.0 Hz, 2H, Ar-H), 7.29-7.27 (d, J = 8.0 Hz, 2H, Ar-H), 3.25-3.19 (q, J = 7.16 Hz, 4H), 2.41 (s, 3H), 1.13-1.10 (t, J = 7.16 Hz, 6H).

RESULTS AND DISCUSSION

From time to time, the development of sulfonamides is a fascinating and informative area in medicinal chemistry. Its functional group has a long and rich history in organic chemistry and drug discovery³⁸. Thus, in the continuation of this study, effort on the sulfonamide template, the synthesis and spectroscopic study of N,N-diethyl substituted amide bearing p-toluene sulfonamide derivatives 2a-k in a two-step approach starting from p-toluenesulfonyl chloride (p-TsCl) precursor was reported. In this present study, p-TsCl was not explored only as a highly economical synthon for preparation of sulfonamide but also as pivotal skeleton for achieving incorporation of amide within such a sulfonamide core structure to obtain N,N-diethyl substituted amide bearing p-toluene sulfonamide derivatives, 2a-k. Firstly, p-toluenesulfonyl chloride (p-TsCl) was made to react with various amino acids under alkaline condition according to a known procedure³⁹ to afford a series of ten arylsulfonamides 1a-j (Fig. 1) and one tosylated sulfonamide 1k. In detail, coupling of p-TsCl with two amino acids whose Nitrogen atom was secondary amine in nature afforded the sulfonamides 1a and 1b in excellent yields of 95.92 and 95.01%, respectively. This reaction was carried out in aqueous sodium carbonate and allowed to stir at room temperature for 4 h for total and effective consumption of the amino acid (monitored with TLC).

In similar manner, equimolar reaction of p-TsCl with eight other amino acids containing primary amino group afforded the corresponding sulfonamides 1c-j in good to excellent yields (69.10-99.00%). The sulfonamides were all worked up via the same technique irrespective of the nature of the amino group that existed here-in. The study up was achieved by acidifying with 2N HCl until the pH 2 was attained. The resulting mixture was kept in freezer chest for proper crystallization, after which it was filtered, washed with buffer (pH 2.2) and vacuum-dried for 12 h at 60°C to obtain crude products, which were purified using column chromatography with chloroform/methanol (9:1) as the eluting solvent. However, tyrosine required double molar proportion of p-TsCl for complete reaction to give 1k in 80.47% yield. The observed crystallization of 1a-k after work-up and refrigeration was contrary to that of α-TsCl where in crystallization could not be achieved until lyophilization was carried out on the obtained solution after refrigeration⁴⁰. This means that α-TsCl resulted in highly polar sulfonamide, while p-TsCl resulted in less polar sulfonamide, which suggested that the position of methyl/methylene group played a significant role in the polar attribute of these type of sulfonamides. This is due to the fact

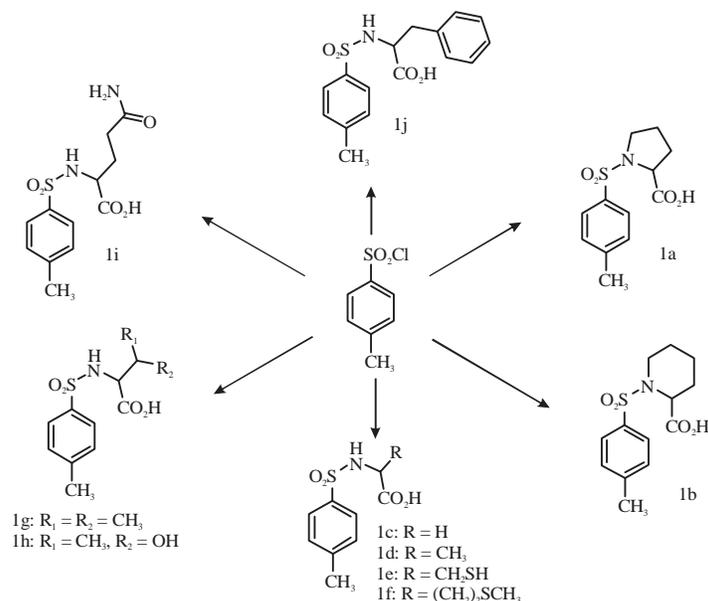


Fig. 1: Synthesis of p-tolylsulfonamide precursors, 1a-j

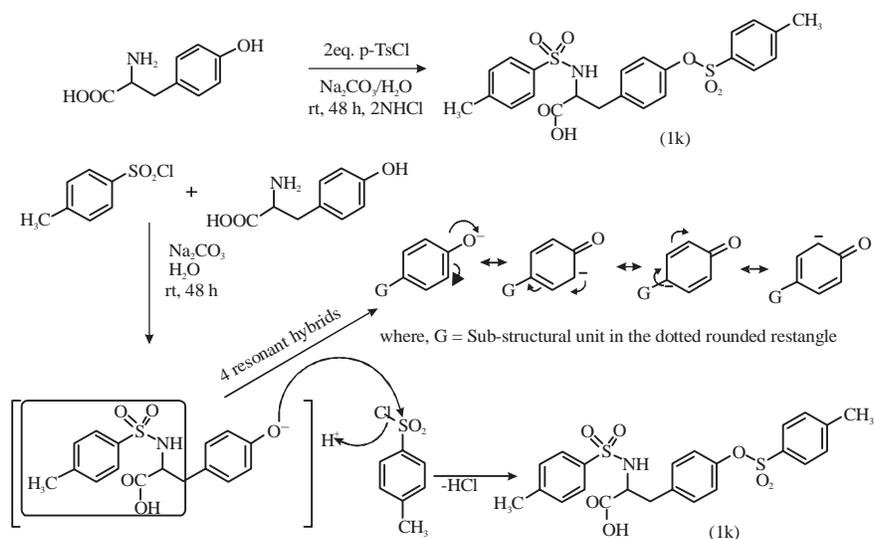


Fig. 2: Mechanism for formation of 2-(4-methylphenylsulfonamido)-3-(4-(tosyloxy)phenyl) propanoic acid, 1k

that in addition to the sulfonylation, tyrosine also experienced tosylation on the phenolic hydroxyl group at the para position of the phenyl ring to give 1k, whose structure was consistent with the assigned ¹H and ¹³C-NMR spectra (Experimental). This unusual reaction in the formation of 1k was as a result of the resonant stabilization of the phenolate anion conjugate base as shown by the reaction path in Fig. 2. This resonant stabilization caused the equilibrium to shift forward, hence, tosylation is highly favoured.

The spectroscopic study was investigated for the structural elucidation using FT-IR, ¹H and ¹³C NMR, mass

spectral and elemental analytical data. The data correlated well with the proposed structures for the synthesized sulfonamides. Nevertheless, 1k was used as representative compound for the spectroscopic explanation. The ¹H-NMR spectrum of 1k in deuterated chloroform showed CH₃ attached to phenyl and tosylate as singlet at δ 2.41 and 2.45 ppm, respectively, while the two protons of CH₂-Ar resonated as two separate doublets of doublets at δ 2.97-2.92 and 3.11-3.06 ppm. The NH and its adjacent neighboring CH resonated as a doublet and a quartet at δ 5.14-5.12 and 4.17 and 4.12 ppm, respectively. All the 12 aromatic protons

were experienced as expected between δ 6.85-6.83 and 7.69-7.67 ppm. These chemical shifts were in concordance with the chemical shifts of aromatic protons recently reported by Navale *et al.*⁴¹ who utilized quinazoline-based framework to prepare novel heterocyclic Schiff bases. The ¹³C-NMR spectrum confirmed 1k to have twenty-three carbon atoms ranging from δ 173.7 ppm (CO) to 21.7 ppm (CH₃) as envisaged. All the eighteen aromatic carbons resonated between δ 149.1 and 122.6 ppm, while the three remaining signals which depicted CH₃ linked to tosylate, CH₂ linked to phenyl (benzylic) and CH linked to NH were observed at δ 21.9, 38.3 and 56.4 ppm, respectively. This was in agreement with the chemical shifts of aromatic carbon reported by Li *et al.*⁴² when they developed a convenient microwave-assisted synthesis of 2-substituted quinazolin-4 (3H)-ones, 2,2-disubstituted 2,3-dihydroquinazolin-4 (1H)-ones 2 and 1H, 3H-quinazolin-2,4-dione. The IR spectrum of 1k exhibited the absorption bands at 1717 and 1559 cm⁻¹ due to the presence of C=O (acid) and C=C, respectively while SO₂ functionality was observed as two bands at 1150 and 1092 cm⁻¹. The carbonyl frequency herein reported (1717 cm⁻¹) was further confirmed by comparing it with the findings of Lewis *et al.*⁴³ who documented the various C=O stretching absorption vibration frequencies in infrared spectra to range between 1685-1758 cm⁻¹. Mass spectrum of 1k showed the base peak at *m/z* 65.0. Although, molecular ion peak was not observed, however, there was an appearance of a fragment *m/z* 443.1, which was as a result of loss of COOH (M⁺-45). Other fragmentation patterns resulted in some other prominent daughter fragments at *m/z* of 171.0, 156.0, 155.0, 134.1 and 92.1 with the intensities of 35, 58, 90, 90 and 64%, respectively. The result of elemental analysis was consistent with that of the proposed structures showing not more than a maximum different of +0.20 between percentage calculated and percentage found for the carbon, hydrogen and nitrogen of the prepared sulfonamides.

Secondly, amidation of *p*-tolylsulfonamide in basic condition gave the N,N-diethylamide substituted *p*-tolylsulfonamide derivatives. We were motivated to synthesize these disubstituted amides based on the earlier findings of Dobek *et al.*⁴⁴ who reported that N,N-disubstituted thiosemicarbazones are more active than their mono and non-substituted counterparts on *S. aureus* and *E. coli*. The reaction optimization study for the amidation was investigated using 1d as representative *p*-tolylsulfonamide in the presence of procedure that involved either sodium hydroxide⁴⁵ or the one that furnished the product via triethyl amine basified condition⁴⁶. The use of sodium hydroxide was

unable to deliver the desired product 2d but rather produced N,N-diethyl-4-methylbenzenesulfonamide 2d₂. This was because nucleophilic propensity of sodium hydroxide led to the cleavage of the S-N bond of the sulfonamide, 1d thereby causing breaking away of amino acid part before subsequent amidation occurred (Fig. 3a). This cleavage, which was initiated with hydroxyl anion, resulted in temporary formation of 4-methyl benzenesulfonic acid, which quickly reacted with diethyl amine to afford 2d₂ as shown in Fig. 3a. This was established by the ¹H-NMR of the product 2d₂ obtained, which experienced a disappearance of the signals of NH, CH and CH₃ protons, which were earlier present in 1d at δ 8.05-8.03, 3.74-3.71 and 1.13-1.12 ppm, respectively. However, when triethyl amine basified condition was used, 1d was synthetically transformed into the expected 2d in excellent yield using one pot two steps amidation approach (Fig. 3b). Hence, the modified Kuethe and Beutner⁴⁶ method was used as the standard optimized condition for the synthesis of N,N-diethyl amide substituted sulfonamides from the corresponding *p*-tolylsulfonamide derivatives.

Therefore, the intermediate arylsulfonamides 1a-k subsequently underwent one pot two steps amidation via modification of a known procedure⁴⁶ to afford the corresponding N,N-diethyl substituted amide 2a-k (Fig. 4). According to Kuethe and Beutner⁴⁶, this method was good for converting aromatic carboxylic acid, such as benzoic acid derivatives to amide. Nevertheless, it is established as a facile method for selective conversion of non-aromatic -COOH within a sulfonamide to the corresponding amide without doing any damage to the existing -SO₂NH- functionality present. This in turn, helped us to achieve our aim of incorporating amide group within a sulfonamide framework. The merits of this approach include higher yields, easy study up, shorter synthetic route because each of the crude intermediates required no purification before taking forward, thus, providing a quick and efficient synthetic route. The 1st step of this method involved treatment of 1a-k with oxalyl chloride in catalytic amount of dimethyl formamide (DMF) for generating acid chloride instead of the common thionyl chloride conventional approach. The chloride ion, which was the reaction initiator and precedential species for the formation of acid chlorides was generated by molecular interaction between oxalyl chloride and DMF via a proposed mechanism (Fig. 5a) similar to that of Swern oxidation⁴⁷. The *in situ* acid chlorides were immediately converted to N,N-diethyl substituted amides 2a-k by subsequent amidation with diethyl amine in basic medium between controlled temperature of -10°C and room temperature.

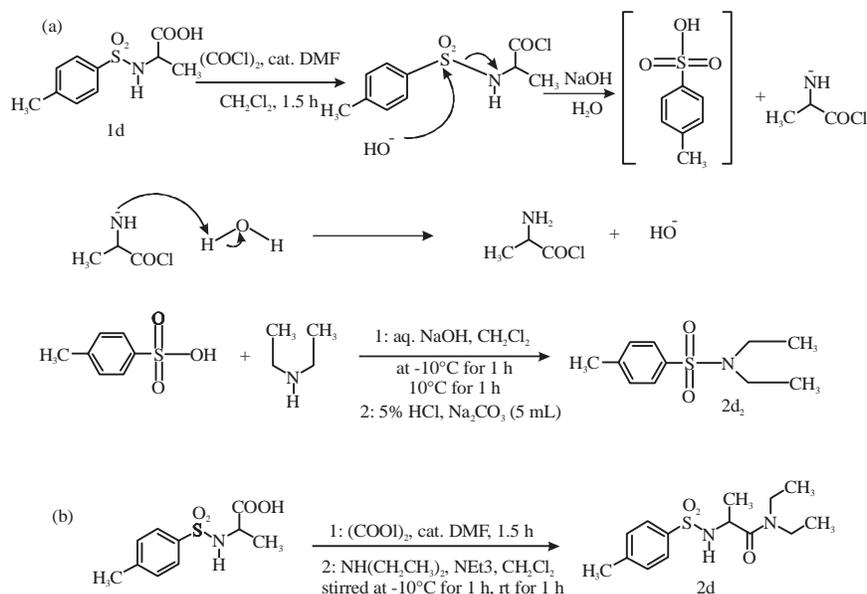


Fig. 3(a-b): Amidation optimization study using sulfonamide, 1d

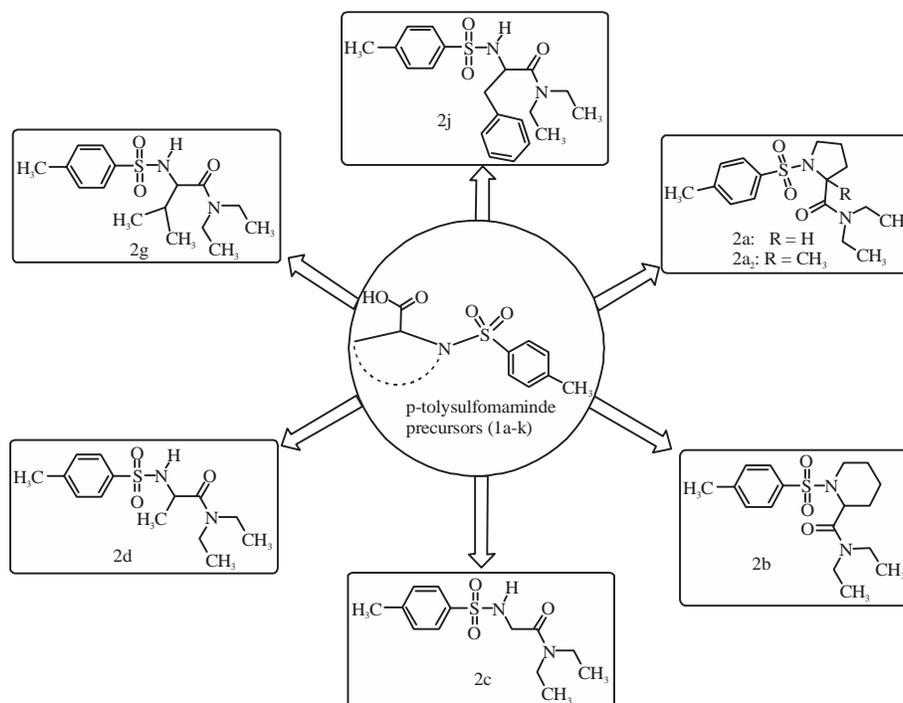


Fig. 4: Synthetic conversion of p-tolysulfonamide intermediates to N,N-diethylamido-s-sulfonamides using DMF and oxalyl chloride in triethyl amine

Moreover, compound 1a unlike other p-tolysulfonamides, gave two different N,N-diethylamide substituted sulfonamides (2a and 2a₂) depending on the nature of work up carried out after the successful amidation has been completed. The worked up of amidated product from 1a in the absence of

methanol gave N,N-diethyl-1-tosylpyrrolidine-2-carboxamide 2a while in the presence of methanol afforded N,N-diethyl-2-methyl-1-tosylpyrrolidine-2-carboxamide 2a₂ (Fig. 5b). This additional methylation experienced in 2a₂ was due to the slight acidic nature of the pyrrolo proton adjacent to the

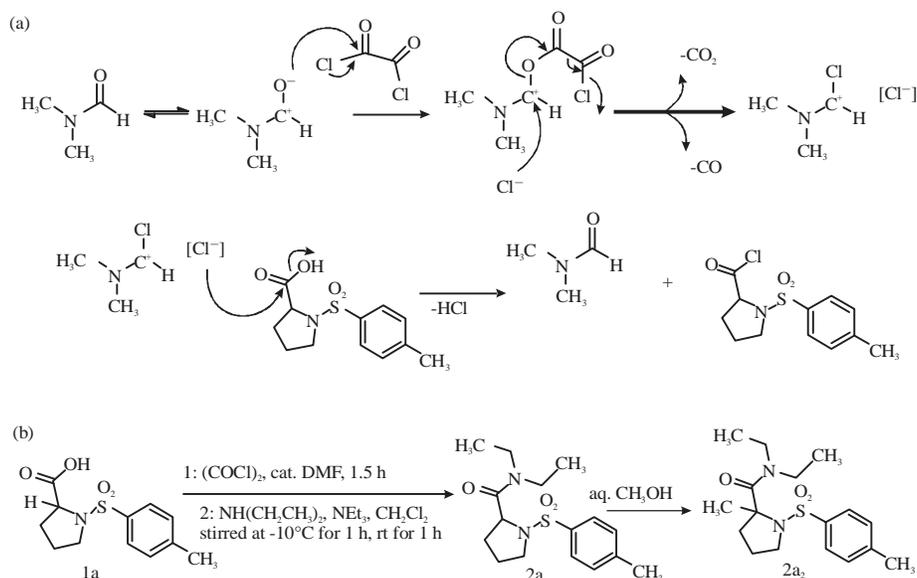


Fig. 5(a-b): Proposed mechanism for chloride ion generation and subsequent amidation

Table 1: Physicochemical parameters of the synthesized compounds

Compound code	Molecular formula	Mol. Wt.	Yield (%)	M.P. ($^\circ\text{C}$)	R_f^b	Elem. Anal. C	Calcd. H (%)	(Percentage of found) N
1a	$\text{C}_{12}\text{H}_{15}\text{NO}_4\text{S}$	269.32	95.92	41-43 ^a	0.82	53.52 (53.68)	5.61 (5.52)	5.20 (5.19)
1b	$\text{C}_{13}\text{H}_{17}\text{NO}_4\text{S}$	283.35	95.01	-	0.89	55.11 (54.90)	6.05 (6.08)	4.94 (5.02)
1c	$\text{C}_9\text{H}_{11}\text{NO}_4\text{S}$	229.26	95.82	120-122	0.47	47.15 (46.90)	4.84 (5.01)	6.11 (5.97)
1d	$\text{C}_{10}\text{H}_{13}\text{NO}_4\text{S}$	243.28	82.57	116-118	0.78	49.37 (49.33)	5.39 (5.41)	5.76 (5.81)
1e	$\text{C}_{10}\text{H}_{13}\text{NO}_4\text{S}_2$	275.35	88.10	161-164	0.39	43.62 (43.55)	4.68 (4.76)	5.11 (5.09)
1f	$\text{C}_{12}\text{H}_{17}\text{NO}_4\text{S}_2$	303.40	69.10	-	0.80	47.51 (47.57)	5.69 (5.65)	4.62 (4.58)
1g	$\text{C}_{12}\text{H}_{17}\text{NO}_4\text{S}$	271.34	94.69	125-126	0.81	53.12 (52.91)	6.32 (6.33)	5.16 (5.08)
1h	$\text{C}_{11}\text{H}_{15}\text{NO}_5\text{S}$	273.31	94.42	90-92	0.62	48.34 (48.37)	5.53 (5.49)	5.12 (5.21)
1i	$\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_5\text{S}$	300.34	82.67	145-146	0.14	47.99 (47.77)	5.37 (5.39)	9.33 (9.04)
1j	$\text{C}_{16}\text{H}_{17}\text{NO}_4\text{S}$	319.38	99.00	139-140	0.76	60.17 (59.97)	5.37 (5.42)	4.39 (4.36)
1k	$\text{C}_{23}\text{H}_{23}\text{NO}_4\text{S}_2$	489.09	80.47	101-103	0.76	56.43 (56.26)	4.74 (4.79)	2.86 (3.04)
2a	$\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_3\text{S}$	324.45	92.30	80-82	0.86	59.23 (57.97)	7.46 (7.20)	8.63 (7.92)
2a ₂	$\text{C}_{17}\text{H}_{26}\text{N}_2\text{O}_3\text{S}$	338.47	91.70	95-96	0.89	60.33 (60.39)	7.74 (7.69)	8.28 (8.23)
2b	$\text{C}_{17}\text{H}_{26}\text{N}_2\text{O}_3\text{S}$	338.47	94.10	127-129	0.92	60.33 (60.37)	7.74 (7.88)	8.28 (8.34)
2c	$\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}_3\text{S}$	284.38	82.70	109-111	0.51	54.91 (54.88)	7.09 (7.11)	9.85 (9.92)
2d	$\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}_3\text{S}$	298.41	77.90	121-124	0.82	56.35 (56.41)	7.43 (7.45)	9.39 (9.34)
2d ₂	$\text{C}_{11}\text{H}_{17}\text{NO}_2\text{S}$	227.33	81.50	188-189	0.55	58.12 (57.09)	7.54 (7.47)	6.16 (6.21)
2g	$\text{C}_{16}\text{H}_{26}\text{N}_2\text{O}_3\text{S}$	326.46	89.40	164-166	0.85	58.87 (58.83)	8.03 (8.11)	8.58 (8.55)
2j	$\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_3\text{S}$	374.51	89.41	164-166	0.80	64.14 (64.09)	7.00 (7.03)	7.48 (7.44)

^bSolvent system: $\text{CHCl}_3/\text{CH}_3\text{OH}$ (9:1, v/v), Mol. Wt: Molecular weight, MP: Melting point

carbonyl group. When the amidated product from 1a was worked up in the presence of methanol as recorded in general procedure, methyl group replaced acidic proton found in between nitrogen and carbonyl group to furnish 2a₂ in 91.7% yield. This was confirmed by presence of three proton singlet of CH_3 at δ 2.42 apart from that of the CH_3 linked to the phenyl group, which occurred at δ 2.39. The physicochemical parameters of the synthesized compounds were as shown in Table 1.

CONCLUSION

A series of p-tolylsulfonamide derivatives have been synthesized by coupling of p-TsCl with some cheap and readily available amino acids and were subsequently brought forward as intermediate precursors in the synthesis of selected N,N-diethyl substituted amido sulfonamides. The methodology discussed in this study did not only provide a new way to design and synthesized a series of

N,N-diethylamide bearing sulfonamides in highly encouraging yields but also demonstrated a more reliable study to achieve such valuable intermediates which might pave way to new series of heterocyclic compounds.

REFERENCES

- Kivela, A.J., J. Kivela, J. Saarnio and S. Parkkila, 2005. Carbonic anhydrases in normal gastrointestinal tract and gastrointestinal tumours. *World J. Gastroenterol.*, 11: 155-163.
- Giguere, S., J.F. Presscott, J.D. Baggot, R.D. Walke and P.M. Dowling, 2006. *Antimicrobial Therapy in Veterinary Medicine*. 4th Edn., Blackwell Publishing Ltd., Oxford, UK.
- LaMarche, M.J., J.A. Leeds, J. Dzink-Fox, K. Gunderson and P. Krastel *et al.*, 2011. 4-Aminothiazolyl analogues of GE2270 A: Antibacterial lead finding. *J. Med. Chem.*, 54: 2517-2521.
- Gomes, J.R.B. and P. Gomes, 2005. Gas-phase acidity of sulfonamides: Implications for reactivity and prodrug design. *Tetrahedron*, 61: 2705-2712.
- Ghorab, M.M., F.A. Ragab, H.I. Heiba, R.K. Arafa and E.M. El-Hossary, 2010. *In vitro* anticancer screening and radiosensitizing evaluation of some new quinolines and pyrimido[4,5-*b*]quinolines bearing a sulfonamide moiety. *Eur. J. Med. Chem.*, 45: 3677-3684.
- Santosh, K., M.S. Niranjana, K.C. Chaluvareddy, C.M. Jamakhandi and D. Kadadevar, 2010. Synthesis and antimicrobial study of some Schiff bases of sulfonamides. *J. Curr. Pharm. Res.*, 1: 39-42.
- Vernier, W.F., W.K.M. Chong, D.A. Rewolinski, S.E. Greasley and T.A. Pauly *et al.*, 2010. Corrigendum to Thioether benzenesulfonamide inhibitors of carbonic anhydrases II and IV: Structure-based drug design, synthesis and biological evaluation [Bioorg. Med. Chem. 18 (2010) 3307]. *Bioorg. Med. Chem.*, 18: 7144-7144.
- Bhaumik, J., R. Weissleder and J.R. McCarthy, 2009. Synthesis and photophysical properties of sulfonamidophenyl porphyrins as models for activatable photosensitizers. *J. Org. Chem.*, 74: 5894-5901.
- Helal, A., S.H. Kim and H.S. Kim, 2010. Thiazole sulfonamide based ratiometric fluorescent chemosensor with a large spectral shift for zinc sensing. *Tetrahedron*, 66: 9925-9932.
- Gong, B., C. Zheng, E. Skrzypczak-Jankun and J. Zhu, 2000. Two-dimensional molecular layers: Interplay of H-bonding and van der Waals interactions in the self-assembly of N,N'-dialkylsulfamides. *Org. Lett.*, 2: 3273-3275.
- Hu, Z.Q. and C.F. Chen, 2006. Self-assembly of aromatic sulfonamide-amide hybridized molecules: Formation of 2D layers and 3D microporous networks in the solid state. *Tetrahedron*, 62: 3446-3454.
- Williams, A.L., S.R. Dandepally, N. Gilyazova, S.M. Witherspoon and G. Ibeanu, 2010. Microwave-assisted synthesis of 4-chloro-N-(naphthalen-1-ylmethyl)-5-(3-(piperazin-1-yl)phenoxy)thiophene-2-sulfonamide (B-355252): A new potentiator of nerve growth factor (NGF)-induced neurite outgrowth. *Tetrahedron*, 66: 9577-9581.
- Meshram, G.A. and V.D. Patil, 2009. A simple and efficient method for sulfonylation of amines, alcohols and phenols with cupric oxide under mild conditions. *Tetrahedron Lett.*, 50: 1117-1121.
- Bornholdt, J., K.W. Fjaere, J. Felding and J.L. Kristensen, 2009. Heterocyclic pentafluorophenyl sulfonate esters as shelf stable alternatives to sulfonyl chlorides. *Tetrahedron*, 65: 9280-9284.
- Barbosa, M.L.D.C., G.M.D.A. Melo, Y.K.C. da Silva, R.D.O. Lopes and E.T. de Souza *et al.*, 2009. Synthesis and pharmacological evaluation of N-phenyl-acetamide sulfonamides designed as novel non-hepatotoxic analgesic candidates. *Eur. J. Med. Chem.*, 44: 3612-3620.
- Argyropoulou, I., A. Geronikaki, P. Vicini and F. Zani, 2009. Synthesis and biological evaluation of sulfonamide thiazole and benzothiazole derivatives as antimicrobial agents. *Arxivoc*, 6: 89-102.
- Humljan, J., M. Kotnik, A. Boniface, T. Solmajer, U. Urleb, D. Blanot and S. Gobec, 2006. A new approach towards peptidosulfonamides: synthesis of potential inhibitors of bacterial peptidoglycan biosynthesis enzymes MurD and MurE. *Tetrahedron*, 62: 10980-10988.
- Da Silva, L.E., P.T. de Sousa Jr., E.N. Maciel, R.K. Nunes, I. Eger, M. Steindel and R.A. Rebelo, 2010. *In vitro* antiprotozoal evaluation of zinc and copper complexes based on sulfonamides containing 8-aminoquinoline ligands. *Lett. Drug Des. Discov.*, 7: 679-685.
- Steurer, M. and C. Bolm, 2010. Synthesis of amino-functionalized sulfonimidamides and their application in the enantioselective Henry reaction. *J. Org. Chem.*, 75: 3301-3310.
- Blank, B.R., P. Alayoglu, W. Engen, J.K. Choi, C.E. Berkman and M.O. Anderson, 2011. N-substituted glutamyl sulfonamides as inhibitors of glutamate carboxypeptidase II (GCP2). *Chem. Biol. Drug Des.*, 77: 241-247.
- Lea, Z.G., Z.C. Chen, Y. Hu and Q.G. Zheng, 2004. Organic reactions in ionic liquids: A simple and highly regioselective N-substitution of pyrrole. *Synthesis*, 12: 1951-1954.
- Li, J.L. and J.T. Liu, 2007. Introducing difluoromethylene sulfonamide group via nucleophilic addition of difluoromethylene anion with aromatic aldehydes. *Tetrahedron*, 63: 898-903.
- Zu, L., J. Wang, H. Li and W. Wang, 2006. A recyclable fluorine (S)-pyrrolidine sulfonamide promoted direct, highly enantioselective Michael addition of ketones and aldehydes to nitroolefins in water. *Org. Lett.*, 8: 3077-3079.

24. Gartner, Z.J., B.N. Tse, R. Grubina, J.B. Doyon, T.M. Snyder and D.R. Liu, 2004. DNA-templated organic synthesis and selection of a library of macrocycles. *Science*, 305: 1601-1605.
25. Schlummer, B. and J.F. Hartwig, 2002. Bronsted acid-catalyzed intramolecular hydroamination of protected alkenylamines. Synthesis of pyrrolidines and piperidines. *Org. Lett.*, 4: 1471-1474.
26. Griffiths-Jones, C.M. and D.W. Knight, 2010. Carbenium ion trapping using sulfonamides: An acid-catalysed synthesis of pyrrolidines by intramolecular hydroamination. *Tetrahedron*, 66: 4150-4166.
27. Zuliani, V., F. Bordi, M. Rivara, C. Silva and F. Vacondio *et al.*, 2003. The role of HB-donor groups in the heterocyclic polar fragment of H₃-antagonists.: I. Synthesis and biological assays. *Il Farmaco*, 58: 891-899.
28. Abbenante, G. and D.P. Fairlie, 2005. Protease inhibitors in the clinic. *Med. Chem.*, 1: 71-104.
29. Liu, F., N.Y. Musadji, F. Lecornue, M.P. Jouannetaud and S. Thibaudeau, 2010. Superacid mediated reactions applied to 4-aminobenzofused sultams and fluorinated 4-aminobenzene sulfonamides synthesis. *Tetrahedron*, 66: 7112-7118.
30. Wang, G.Y., J.B. Hu and G. Zhao, 2004. Enantioselective reduction of α -keto esters to 1,2-diols using the NaBH₄/Me₃SiCl system catalyzed by polymer-supported chiral sulfonamide. *Tetrahedron: Asymmetry*, 15: 807-810.
31. Salvatore, R.N., C.H. Yoon and K.W. Jung, 2001. Synthesis of secondary amines. *Tetrahedron*, 57: 7785-7811.
32. Canesi, S., D. Bouchu and M.A. Ciufolini, 2004. Fully stereocontrolled total syntheses of (-)-Cylindricine C and (-)-2-Epicylindricine C: A departure in sulfonamide chemistry. *Angew. Chem. Int. Edn.*, 43: 4336-4338.
33. Weinreb, S.M. 2003. Lepadiformine: A case study of the value of total synthesis in natural product structure elucidation. *Acc. Chem. Res.*, 36: 59-65.
34. Schar, P., S. Cren and P. Renaud, 2006. Tricyclic marine alkaloids: Synthetic approaches to cylindricines, lepadiformine and fasicularin. *CHIMIA Int. J. Chem.*, 60: 131-141.
35. Morton, D., S. Leach, C. Cordier, S. Warriner and A. Nelson, 2009. Synthesis of natural-product-like molecules with over eighty distinct scaffolds. *Angew. Chem. Int. Edn.*, 48: 104-109.
36. Naik, S., G. Bhattacharjya, B. Talukdar and B.K. Patel, 2004. Chemoselective acylation of amines in aqueous media. *Eur. J. Org. Chem.*, 6: 1254-1260.
37. Katritzky, A.R., C. Cai and S.K. Singh, 2006. Efficient microwave access to polysubstituted amidines from imidoylbenzotriazoles. *J. Org. Chem.*, 71: 3375-3380.
38. Ajani, O.O., O.B. Familoni, D.V. Aderohunmu, K.O. Ogunniran, J.A. Adekoya and I.O. Olanrewaju, 2015. Comparative study of the antibacterial activity of N, N-diethylamido substituted p-toluenesulfonamides to their α -toluenesulfonamide counterparts. *Pak. J. Biol. Sci.*, 18: 166-172.
39. Ajani, O.O., O.B. Familoni, F. Wu, J.O. Echeme and Z. Sujiang, 2012. Room temperature synthesis and antibacterial activity of new sulfonamides containing N,N-diethyl-substituted amido moieties. *Int. J. Med. Chem.*, Vol. 2012. 10.1155/2012/367815
40. Ajani, O.O., O.B. Familoni, F. Wu and J.O. Echeme, 2013. Eco-friendly room temperature synthesis in aqueous medium: An expeditious approach to new α -tolylsulfonamides bearing N,N-diethyl amide moieties. *Open Organiz. Chem. J.*, 7: 1-11.
41. Navale, V., R. Shinde, S. Patil, A. Vibhute and S. Zangade, 2016. Quinazoline based synthesis of some novel heterocyclic Schiff bases. *J. Adv. Chem. Sci.*, 2: 201-203.
42. Li, F., Y. Feng, Q. Meng, W. Li, Z. Li, Q. Wang and F. Tao, 2007. An efficient construction of quinazolin-4(3H)-ones under microwave irradiation. *Arkivoc*, 1: 40-50.
43. Lewis, R.N., R.N. McElhaney, W. Pohle and H.H. Mantsch, 1994. Components of the carbonyl stretching band in the infrared spectra of hydrated 1,2-diacylglycerolipid bilayers: A reevaluation. *Biophys. J.*, 67: 2367-2375.
44. Dobek, A.S., D.L. Klayman, E.T. Dickson, J.P. Scovill and E.C. Tramont, 1980. Inhibition of clinically significant bacterial organisms *in vitro* by 2-acetylpyridine thiosemicarbazones. *Antimicrob. Agents Chemother.*, 18: 27-36.
45. Speziale, A.J. and R.C. Freeman, 1961. N,N-diethyl-1, 2, 2-trichlorovinylamine. *Org. Syn.*, 41: 21-23.
46. Kuethe, J.T. and G.L. Beutner, 2009. Synthesis of 2-arylindole-4-carboxylic amides: [2-(4-Fluorophenyl)-1H-indol-4-yl]-1-pyrrolidinylmethanone. *Org. Syn.*, 86: 92-104.
47. Kawaguchi, T., H. Miyata, K. Ataka, K. Mae and J.I. Yoshida, 2005. Room-temperature swern oxidations by using a microscale flow system. *Angew. Chem. Int. Edn.*, 44: 2413-2416.