ISSN 1996-5052

Current Research in Chemistry

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OPEN ACCESS Current Research in Chemistry

ISSN 1996-5052
DOI: 10.3923/crc.2016.10.20

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

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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, ^{1}H-NMR, ^{13}C-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: May 22, 2016 Accepted: June 05, 2016 Published: June 15, 2016

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., 8: 10-20.

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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 gastrointestinal[1] and urinary tract infections[2]. In fact, sulfonamide which is the organic framework of main focus in this present study belongs to the family of sulfur-containing compounds with -SO_2NH- functionality which are earlier referred as to as the sulfa drugs[3]. The characterization of sulfonamides as chemotherapeutics is more than half a century old[4]. Since, then, the sulfonamide group has been found as a key structural motif shared by a large number of bioactive compounds[5-7]. 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 photosensitizers[8], chemosensors with selective fluorescence enhancement among others[9]. Sulfonamide containing moieties are reported to be self-assembled into robust two dimensional molecular layers[10] as well as being valuable building block for higher order superstructures[11].

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 amine[12], substituted aniline[13], piperidine[14], ethanamine[15], benzo[d]thiazol-2-amine[16], dimethyl 2-aminopentanedioate[17], 8-aminoquinoline[18], cyclohexanamine[19], diprotected glutamic acid[20], pyrrole[21] and morpholine[22] to afford the respective sulfonamide products. Many derivatives of sulfonamide have been explored as important starting materials and reactive intermediates in various organic syntheses[23-25]. This authenticates their well-established utility in the synthesis of pyrrolidines[26], isothiourea[27], secondary amine[28], superacid mediated reaction[29], enantioselective reduction of α-ketoester[30] and monoalkylation of amino group[31]. It has also proved to be vital precursor in the total synthesis of some natural product, such as (-)-cylindricine[32], lepadiformine[33], fasicularin[34] and natural-product-like molecules[35].

In a similar manner, amide formation is a fundamental reaction of great interest in organic chemistry[36]. 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 synthesis[37]. 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 ^{1}H-NMR spectra were recorded in either $CDCl_3$ or DMSO-d_6 on NMR Bruker DP×400 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 $CHCl_3$/CH_3OH (9:1) solvent system and Merck silica gel F (Mesh 200-300). Organic solutions were dried over anhydrous Na_2SO_4 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 Na_2CO_3 (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 $CHCl_3$/CH_3OH 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 (SO_2 two bands), 662 (Ar-H). ^{1}H-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 ^{1}H-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×CH arom.), 126.8 (2×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). ^{1}H-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). ^{1}H-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). ^{1}H-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). ^{1}H-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). ^{1}H-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 ^{1}H-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). ^{1}H-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). ^{1}H-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×CH arom.), 129.6 (2×CH arom.), 128.8 (2×CH arom.), 127.4 (2×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 (SO_2 two bands), 669 (Ar-H). The ^{1}H-NMR (400 MHz, $CDCl_3$): 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, J_1 = 5.2 Hz, J_2 = 20.0 Hz, 1H), 2.97-2.92 (dd, J_1 = 6.8 Hz, J_2 = 20.0 Hz, 1H), 2.45 (s, 3H), 2.41 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): 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 CH_2), 21.9 (CH_3 linked to OSO_2-Ar), 21.7 (CH_3 linked to SO_2-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 cautionly 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 N_2 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/N_2 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), 16 78 (C=O of amide), 1609 (C=C), 1155, 1107 (SO_2 two bands), 669 (Ar-H). ^{1}H-NMR (400 MHz, $CDCl_3$): 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, J_1 = 3.6 Hz, J_2 = 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 ($2a_2$): The IR: 2949 (CH arom.), 2860 (CH aliphatic), 1713 (C=O of amide), 1601 (C=C), 1159, 1115 (SO_2 two bands), 654 (Ar-H). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.76-7.73 (dd, J_1 = 6.0 Hz, J_2 = 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, J_1 = 4.0Hz, J_2 = 11.88 Hz, 1H), 4.26-4.24 (dd, J_1 = 3.6 Hz, J_2 = 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), 1.09-105 (t, J = 7.12 Hz, 3H).

N,N-diethyl-1-tosylpiperidine-2-carboxamide (2b): The ^{1}H-NMR (400 MHz, $CDCl_3$): 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 (SO_2 two bands), 694 (Ar-H). ^{1}H-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), 5.80 (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 (SO_2 two bands), 677 (Ar-H). The ^{1}H-NMR (400 MHz, $CDCl_3$): 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 (SO_2 two bands), 689 (Ar-H). The ^{1}H-NMR (400 MHz, $CDCl_3$): 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, J_1 = 4.22 Hz, J_2 = 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 (SO_2 two bands), 685 (Ar-H).^{1}H-NMR (400 MHz, $CDCl_3$): 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 ($2d_2$): 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 ($2d_2$). The IR: 2980 (CH aliphatic), 2876 (CH aromatic), 1632 (C=C), 1148, 1112 (SO_2 two bands), 670 (Ar-H). The ^{1}H-NMR (400 MHz, $CDCl_3$): 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 discovery[38]. 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 procedure[39] 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 refrigeration[40]. 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

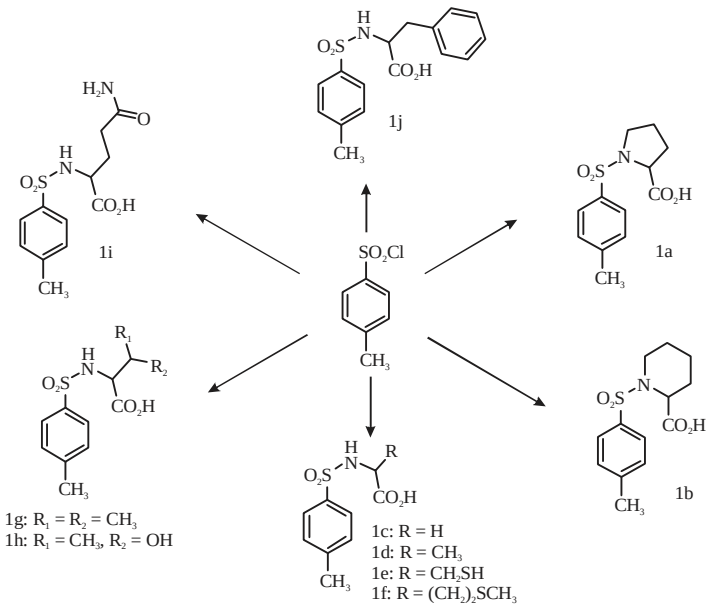

Fig. 1: Synthesis of p-tolylsulfonamide precursors, 1a-j

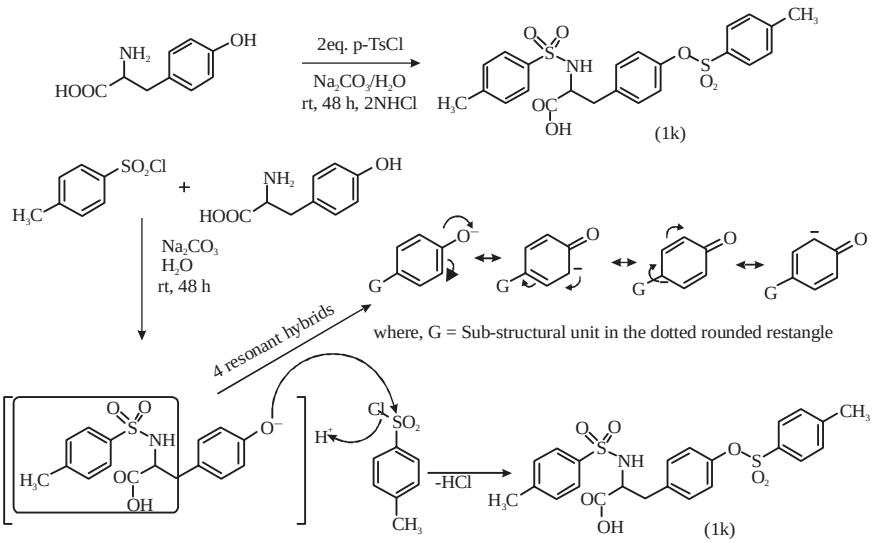

Fig. 2: Mechanism for formation of 2-(4-methylphenylsulfonamido)-3-(4-(tosyloxy)phenyl) propanoic acid, 1k

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 ^{1}H and ^{13}C-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, ^{1}H and ^{13}C 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 ^{1}H-NMR spectrum of 1k in deuterated chloroform showed CH_3 attached to phenyl and tosylate as singlet at d 2.41 and 2.45 ppm, respectively, while the two protons of CH_2-Ar resonated as two separate doublets of doublets at d 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 d 5.14-5.12 and 4.17 and 4.12 ppm, respectively. All the 12 aromatic protons

were experienced as expected between d 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 ^{13}C-NMR spectrum confirmed 1k to have twenty-three carbon atoms ranging from d 173.7 ppm (CO) to 21.7 ppm (CH_3) as envisaged. All the eighteen aromatic carbons resonated between d 149.1 and 122.6 ppm, while the three remaining signals which depicted CH_3 linked to tosylate, CH_2 linked to phenyl (benzylic) and CH linked to NH were observed at d 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 SO_2 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 synthesized 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 hydroxide[45] or the one that furnished the product via triethyl amine basified condition[46]. The use of sodium hydroxide was unable to deliver the desired product 2d but rather produced N,N-diethyl-4-methylbenzenesulfonamide $2d_2$. 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 $2d_2$ as shown in Fig. 3a. This was established by the ^{1}H-NMR of the product $2d_2$ obtained, which experienced a disappearance of the signals of NH, CH and CH_3 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 Beutner[46] 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 procedure[46] to afford the corresponding N,N-diethyl substituted amide 2a-k (Fig. 4). According to Kuethe and Beutner[46], 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 -SO_2NH- 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 oxidation[47]. 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.

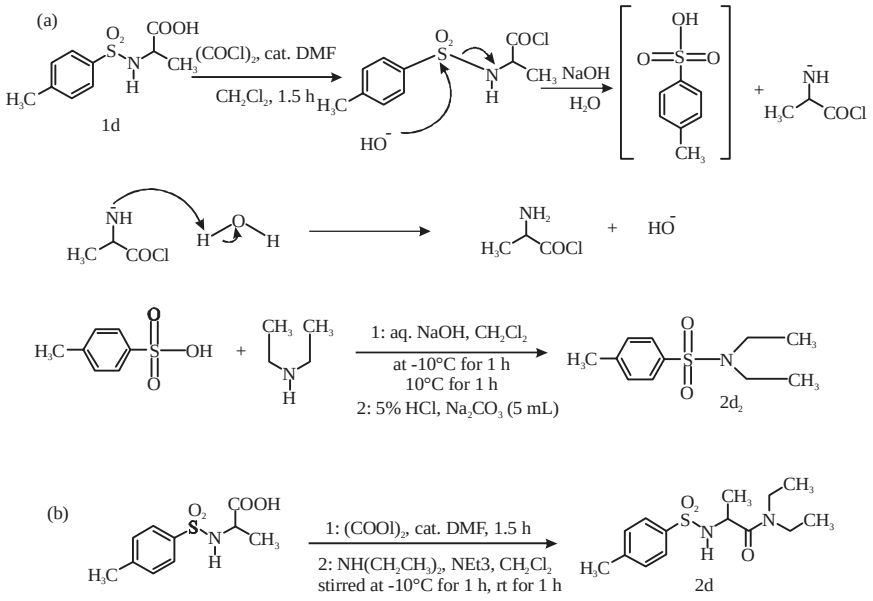

Fig. 3(a-b): Amidation optimization study using sulfonamide, 1d

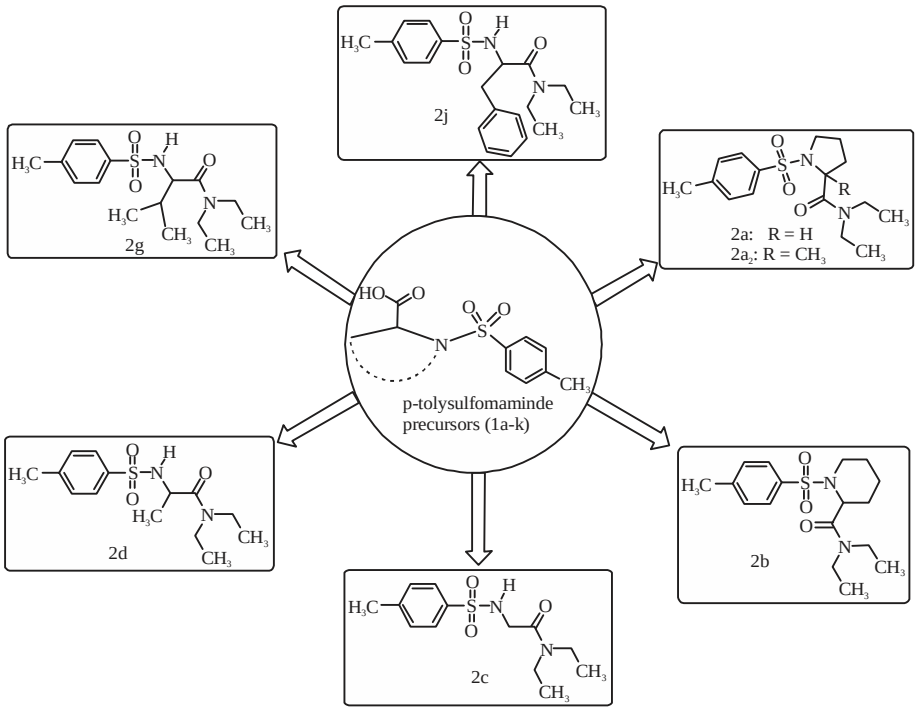

Fig. 4: Synthetic conversion of p-tolylsulfonamide intermediates to N,N-diethylamido-s-sulfonamides using DMF and oxalyl chloride in triethyl amine

Moreover, compound 1a unlike other p-tolylsulfonamides, gave two different N,N-diethylamide substituted sulfonamides (2a and $2a_2$) 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 $2a_2$ (Fig. 5b). This additional methylation experienced in $2a_2$ was due to the slight acidic nature of the pyrrolo proton adjacent to the

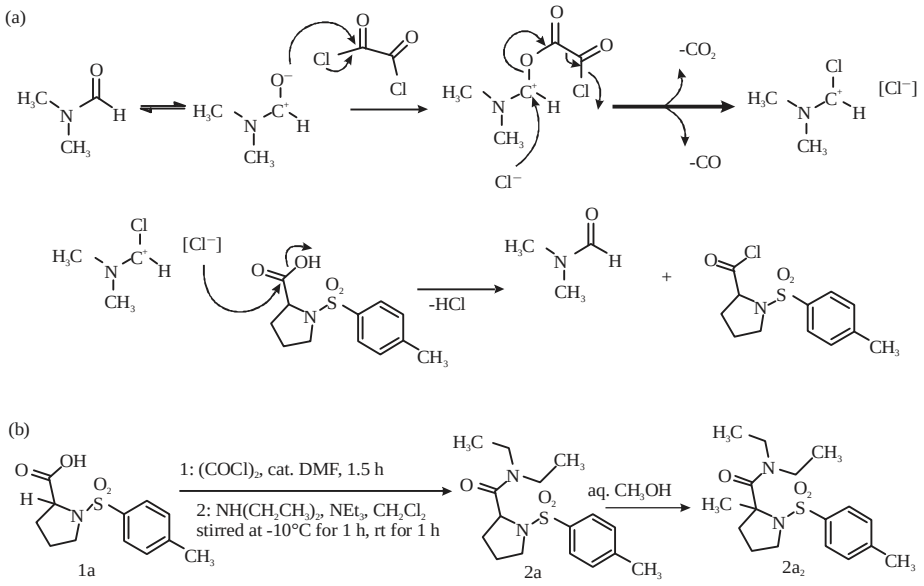

Fig. 5(a-b): Proposed mechanism for chloride ion generation and subsequent amidation

Table 1: Physicochemical parameters of the synthesized compounds

Compound code	Molecular formula	Mol. Wt.	Yield (%)	M.P. (°C)	R_f[b]	Elem. Anal. C	Calcd. H (%)	(Percentage of found) N
1a	$C_{12}H_{15}NO_4S$	269.32	95.92	41-43[a]	0.82	53.52 (53.68)	5.61 (5.52)	5.20 (5.19)
1b	$C_{13}H_{17}NO_4S$	283.35	95.01	-	0.89	55.11 (54.90)	6.05 (6.08)	4.94 (5.02)
1c	$C_9H_{11}NO_4S$	229.26	95.82	120-122	0.47	47.15 (46.90)	4.84 (5.01)	6.11 (5.97)
1d	$C_{10}H_{13}NO_4S$	243.28	82.57	116-118	0.78	49.37 (49.33)	5.39 (5.41)	5.76 (5.81)
1e	$C_{10}H_{13}NO_4S_2$	275.35	88.10	161-164	0.39	43.62 (43.55)	4.68 (4.76)	5.11 (5.09)
1f	$C_{12}H_{17}NO_4S_2$	303.40	69.10	-	0.80	47.51 (47.57)	5.69 (5.65)	4.62 (4.58)
1g	$C_{12}H_{17}NO_4S$	271.34	94.69	125-126	0.81	53.12 (52.91)	6.32 (6.33)	5.16 (5.08)
1h	$C_{11}H_{15}NO_5S$	273.31	94.42	90-92	0.62	48.34 (48.37)	5.53 (5.49)	5.12 (5.21)
1i	$C_{12}H_{16}N_2O_5S$	300.34	82.67	145-146	0.14	47.99 (47.77)	5.37 (5.39)	9.33 (9.04)
1j	$C_{16}H_{17}NO_4S$	319.38	99.00	139-140	0.76	60.17 (59.97)	5.37 (5.42)	4.39 (4.36)
1k	$C_{23}H_{23}NO_7S_2$	489.09	80.47	101-103	0.76	56.43 (56.26)	4.74 (4.79)	2.86 (3.04)
2a	$C_{16}H_{24}N_2O_3S$	324.45	92.30	80-82	0.86	59.23 (57.97)	7.46 (7.20)	8.63 (7.92)
$2a_2$	$C_{17}H_{26}N_2O_3S$	338.47	91.70	95-96	0.89	60.33 (60.39)	7.74 (7.69)	8.28 (8.23)
2b	$C_{17}H_{26}N_2O_3S$	338.47	94.10	127-129	0.92	60.33 (60.37)	7.74 (7.88)	8.28 (8.34)
2c	$C_{13}H_{20}N_2O_3S$	284.38	82.70	109-111	0.51	54.91 (54.88)	7.09 (7.11)	9.85 (9.92)
2d	$C_{14}H_{22}N_2O_3S$	298.41	77.90	121-124	0.82	56.35 (56.41)	7.43 (7.45)	9.39 (9.34)
$2d_2$	$C_{11}H_{17}NO_2S$	227.33	81.50	188-189	0.55	58.12 (57.09	7.54 (7.47)	6.16 (6.21)
2g	$C_{16}H_{26}N_2O_3S$	326.46	89.40	164-166	0.85	58.87 (58.83)	8.03 (8.11)	8.58 (8.55)
2j	$C_{20}H_{26}N_2O_3S$	374.51	89.41	164-166	0.80	64.14 (64.09)	7.00 (7.03)	7.48 (7.44)

[b]Solvent system: $CHCl_3/CH_3OH$ (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 $2a_2$ 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.

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