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SYNTHESIS OF PYRROLYL AND PYRAZOLYL SULFONAMIDES

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A new class of pyrrolyl and pyrazolyl sulfonamides was prepared from styrene-ω-sulfonanilides by treatment with tosylmethyl isocyanide and diazomethane, respectively.

Keywords: diazomethane, pyrazolylsulfonamide, pyrrolylsulfonamide, styrene-ω-sulfonanilides, tosylmethyl isocyanide.

Scientific efforts have continuously been directed towards the design and synthesis of five-membered heterocycles because of their utility as pharmacological agents. Netropsin and distamycin are pyrrole polyamides and are naturally occurring anticancer antibiotics [1]. Multistep synthetic routes for 3,4-di-substituted pyrroles have been reported either by coupling of imines and nitroalkanes or using Friedel–Craft's acylation with an electron-withdrawing group on pyrrole nitrogen or 3,4-silylated precursors [2]. Pyrroles have also been prepared from Michael acceptors and tosylmethyl isocyanide (TosMIC) [3, 4]. Several pyrazole derivatives received increased attention due to their biological activities as potential HIV-1 inhibitors [5], insecticides [6], fungicides [6], antiviral [7], anti-inflammatory [8], antiobesity [9], and anticancer agents [10]. Among the different known methods for the synthesis of pyrazoles, Huisgen's 1,3-dipolar cycloaddition is a versatile one [11]. Recent syntheses of pyrazoles *via* 1,3-dipolar cycloaddition includes reaction of nitrile imines and alkynes [12] or enamines [13], hydrazones and nitroolefins [14], diazo compounds and alkynes [15], and azomethine imines and alkynes [16]. We have exploited various activated olefins for the synthesis of a variety of mono- and bis-heterocycles [17, 18]. However, there are no reports to our knowledge about the use of styrene sulfonamides for the development of five-membered heterocycles.

The present communication deals with the synthesis of pyrrolyl and pyrazolyl sulfonamides from styrene-ω-sulfonanilides **1a-c**. The compounds **1a-c** were prepared by the Knoevenagel condensation of aryl-aminosulfonylacetic acids with arylaldehydes. The arylaminosulfonylacetic acids were obtained by the well-known chain of reactions from substituted anilines [19].

The olefin group present in compounds **1a-c** was exploited to develop pyrrole and pyrazoline rings. Treatment of compounds **1a-c** with TosMIC gave 4-aryl-3-arylaminosulfonylpyrroles **2a-c**. The ^{1}H NMR spectrum of compound **2a** showed two singlets at 6.56 and 7.17 ppm due to H-2 and H-5 protons of the pyrrole ring in addition to two broad singlets at 8.41 and 10.45 ppm due to SO_2NH and NH fragments. The latter signals disappeared by deuteration. Similarly, 1,3-dipolar cycloaddition of diazomethane to compounds **1a-c** at a temperature of about -20°C produced 4-aryl-3-arylaminosulfonyl-1-methylpyrazolines **3a-c**. It appears that *N*-methylation also took place during the course of cyclization.

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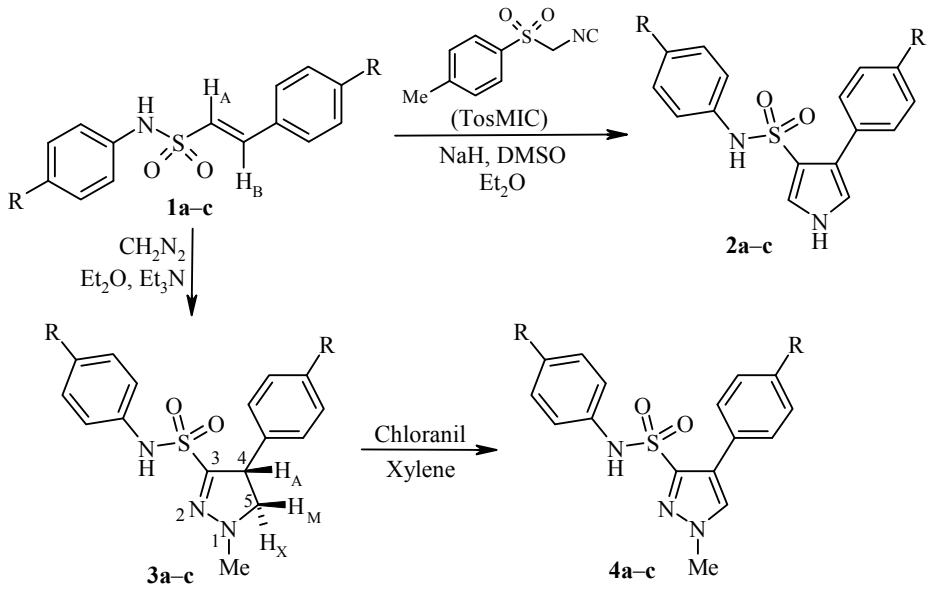

a R = H, **b** R = Me, **c** R = Cl

The ^{1}H NMR spectrum of compound **3a** showed the AMX splitting pattern for methine and methylene protons of pyrazoline ring. The three double doublets observed at 4.22, 3.94, and 3.55 ppm were assigned to pyrazoline ring protons H_A, H_M, and H_X, respectively. The coupling constants indicated that H_A and H_M are in *cis*, H_A and H_X in *trans*, and H_M and H_X in geminal position to each other. A sharp singlet was observed at 3.14 ppm due to NCH_3 group. Apart from these, a broad singlet was observed at 8.37 ppm due to NH, which disappeared on deuteration. Aromatization of compounds **3a-c** with chloranil in xylene resulted in 4-aryl-3-arylaminosulfonyl-1-methylpyrazoles **4a-c**. The absence of the AMX splitting pattern confirmed the formation of compounds **4a-c**. The ^{1}H NMR spectrum of compound **4a** displayed two sharp singlets due to the NCH_3 group and the H-5 proton (overlapping with multiplet signal of phenyl protons), and a broad singlet due to NH proton. The signal due to NH disappeared by deuteration. The structures of the compounds were further established by IR and ^{13}C NMR spectra.

Thus, a simple substrate, styrene-ω-sulfonanilide, was exploited to obtain new sulfonamide-linked pyrroles and pyrazoles adopting the 1,3-dipolar cycloaddition methodology.

EXPERIMENTAL

The IR spectra were recorded on a Thermo Nicolet IR 200 FT-IR spectrometer in KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Spectrospin instrument (400 and 100 MHz, respectively) in DMSO-d_6 using TMS as internal standard. The elemental microanalyses were performed on a Perkin Elmer 240C Elemental Analyzer. Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The purity of the compounds was checked by TLC (silica gel H, BDH, eluent EtOAc–hexane, 1:3). The starting arylaminosulfonylacetic acids were prepared by the literature procedure [19].

Styrene-ω-sulfonanilides 1a-c (General Method). A mixture of arylaldehyde (1 mmol), pyridine (4 ml), $AcONH_4$ (1.00 g, 13 mmol), arylaminosulfonylacetic acid (0.21 g, 1 mmol), and toluene (25 ml) were refluxed for 20–24 h with azeotropic removal of water. The solution was cooled and washed successively with dilute HCl, dilute Na_2SO_3, and brine. Then it was extracted with 10% KOH. The potassium salt of styrene sulfonamide was separated as oil with the aqueous phase. The two-phase aqueous extract was washed with ether

and acidified with HCl. Then, it was extracted with ether. Removal of the solvent under vacuum furnished a solid which on recrystallization from cyclohexane gave compounds **1a-c**.

(*E*)-*N*,2-Diphenylethenesulfonamide (1a). Yield 0.20 g (77%). White solid; mp 108-112°C (mp 113°C [19]). IR spectrum, ν, cm^{-1}: 3332 (NH), 1632 (C=C), 1317, 1138 (SO_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.45 (1H, br. s, NH); 8.04 (1H, d, *J* = 14.7, H_A); 7.84 (1H, d, *J* = 14.7, H_B); 7.22-7.38 (10H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 145.4 (CH_A); 131.3 (CH_B); 139.3, 136.1, 134.2, 133.8, 131.2, 126.7, 125.6, 124.3 (C Ph). Found, %: C 64.75; H 5.01; N 5.48. $C_{14}H_{13}NO_2S$. Calculated, %: C 64.84; H 5.05; N 5.40.

(*E*)-*N*,2-Bis(4-methylphenyl)ethenesulfonamide (1b). Yield 0.23 g (83%). White solid; mp 124-126°C. IR spectrum, ν, cm^{-1}: 3348 (NH), 1625 (C=C), 1320, 1143 (SO_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.48 (1H, br. s, NH); 8.02 (1H, d, *J* = 14.6, H_A); 7.87 (1H, d, *J* = 14.6, H_B); 7.15–7.38 (8H, m, H Ar); 2.39 (3H, s, CH_3), 2.37 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 144.6 (CH_A); 131.5 (CH_B); 137.2, 136.8, 133.7, 132.5, 130.9, 127.4, 124.8, 124.2 (C Ar); 23.7 (CH_3); 23.5 (CH_3). Found, %: C 66.93; H 5.87; N 4.82. $C_{16}H_{17}NO_2S$. Calculated, %: C 66.87; H 5.96; N 4.87.

(*E*)-*N*,2-Bis(4-chlorophenyl)ethenesulfonamide (1c). Yield 0.25 g (77%). White solid; mp 116-118°C. IR spectrum, ν, cm^{-1}: 3341 (NH), 1628 (C=C), 1323, 1146 (SO_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.42 (1H, br. s, NH); 8.08 (1H, d, *J* = 14.8, H_A); 7.89 (1H, d, *J* = 14.8, H_B); 7.25-7.39 (8H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 146.7 (CH_A); 131.8 (CH_B); 138.4, 136.2, 131.8, 131.4, 129.7, 129.5, 126.5, 126.1, 124.5 (C Ar). Found, %: C 51.28; H 3.35; N 4.32. $C_{14}H_{11}Cl_2NO_2S$. Calculated, %: C 51.23; H 3.38; N 4.27.

4-Aryl-3-arylaminosulfonylpyrroles 2a-c (General Method). In a 100 ml two-necked round-bottomed flask fitted with a calcium chloride guard-tube and a septum and equipped with a magnetic stirrer, NaH (0.06 g, 2.5 mmol) in abs. Et_2O (8 ml) was stirred at rt for 20 min. To this, a mixture of TosMIC (0.97 g, 5.0 mmol) and compound **1a-c** (1.29 g, 5.0 mmol) in DMSO (8 ml) and abs. Et_2O (4 ml) was added dropwise *via* a syringe. The stirring was continued for another 18-20 h, and the whole was diluted with H_2O. It was extracted with Et_2O and dried over anhydrous Na_2SO_4. Removal of the solvent *in vacuo* gave a crude product, which was purified by column chromatography (eluent EtOAc–hexane, 1:3).

4-Phenyl-3-phenylaminosulfonylpyrrole (2a). Yield 1.02 g (69%). White solid; mp 125-127°C. IR spectrum, ν, cm^{-1}: 3235 (NH), 1621 (C=C), 1335, 1147 (SO_2). ^1H NMR spectrum, δ, ppm: 10.45 (1H, br. s, NH); 8.41 (1H, br. s, SO_2NH); 7.22-7.82 (10H, m, H Ph); 7.17 (1H, s, H-5); 6.56 (1H, s, H-2). ^{13}C NMR spectrum, δ, ppm: 137.8, 135.9, 131.2, 130.8, 128.3, 126.8, 126.2, 122.8 (C Ph); 120.5 (C-5); 115.7 (C-2); 105.8 (C-4); 104.5 (C-3). Found, %: C 64.53; H 4.67; N 9.32. $C_{16}H_{14}N_2O_2S$. Calculated, %: C 64.41; H 4.73; N 9.39.

4-(4-Methylphenyl)-3-(4-methylphenyl)aminosulfonylpyrrole (2b). Yield 1.06 g (65%). White solid; mp 146-148°C. IR spectrum, ν, cm^{-1}: 3238 (NH), 1625 (C=C), 1339, 1132 (SO_2). ^1H NMR spectrum, δ, ppm: 10.44 (1H, br. s, NH); 8.43 (1H, br. s, SO_2NH); 7.18-7.86 (8H, m, H Ar); 7.13 (1H, s, H-2); 6.68 (1H, s, H-5); 2.34 (3H, s, CH_3); 2.32 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 138.1, 136.5, 131.8, 130.5, 128.8, 127.4, 125.9, 123.6 (C Ar); 119.8 (C-5); 114.2 (C-2); 105.9 (C-4); 104.7 (C-3); 23.4 (CH_3); 23.1 (CH_3). Found, %: C 66.14; H 5.61; N 8.66. $C_{18}H_{18}N_2O_2S$. Calculated, %: C 66.23; H 5.56; N 8.58.

4-(4-Chlorophenyl)-3-(4-chlorophenyl)aminosulfonylpyrrole (2c). Yield 1.24 g (68%). White solid; mp 163-165°C. IR spectrum, ν, cm^{-1}: 3343 (NH), 1618 (C=C), 1337, 1143 (SO_2). ^1H NMR spectrum, δ, ppm: 10.47 (1H, br. s, NH); 8.45 (1H, br. s, SO_2NH); 7.25–7.91 (8H, m, H Ar); 7.23 (1H, s, H-5); 6.54 (1H, s, H-2). ^{13}C NMR spectrum, δ, ppm: 137.5, 136.8, 130.1, 129.7, 128.9, 128.8, 122.2, 121.9 (C Ar); 117.5 (C-5); 113.2 (C-2); 106.4 (C-4); 102.1 (C-3). Found, %: C 52.45; H 3.32; N 7.71. $C_{16}H_{12}Cl_2N_2O_2S$. Calculated, %: C 52.33; H 3.29; N 7.63.

4-Aryl-3-arylaminosulfonyl-1-methylpyrazolines 3a-c (General Method). To a cooled solution of compound **1a-c** (0.64 g, 2.5 mmol) in CH_2Cl_2 (10 ml), 0.4 M Et_2O solution of CH_2N_2 (20 ml) and Et_3N (0.06 g, 0.6 mmol) were added. The reaction mixture was kept at -20 to -15°C temperature for 40-48 h. The solvent was removed under reduced pressure. The resultant solid was purified by column chromatography (eluent EtOAc–hexane, 1:3).

1-Methyl-4-phenyl-3-phenylaminosulfonylpyrazoline (3a). Yield 0.55 g (71%). White solid; mp 136-138°C. IR spectrum, ν, cm^{-1}: 3327 (NH), 1589 (C=N), 1335, 1141 (SO_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.37 (1H, br. s, NH); 7.02-7.33 (10H, m, H Ph); 4.22 (1H, dd, J_{AM} = 12.0, J_{AX} = 6.9, H_A); 3.94 (1H, dd, J_{AM} = 12.0, J_{MX} = 10.9, H_M); 3.55 (1H, dd, J_{AX} = 6.9, J_{MX} = 10.9, H_X); 3.14 (3H, s, NCH_3). ^{13}C NMR spectrum, δ, ppm: 137.5, 136.8, 130.1, 129.7, 128.9, 128.8, 122.2, 121.9 (C Ph); 117.5 (C-5); 113.2 (C-2); 106.4 (C-4); 102.1 (C-3). Found, %: C 61.04; H 5.43; N 13.20. $C_{16}H_{17}N_3O_2S$. Calculated, %: C 60.93; H 5.43; N 13.32.

1-Methyl-4-(4-methylphenyl)-3-(4-methylphenyl)aminosulfonylpyrazoline (3b). Yield 0.61 g (72%). White solid; mp 152-154°C. IR spectrum, ν, cm^{-1}: 3342 (NH), 1594 (C=N), 1340, 1138 (SO_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.45 (1H, br. s, NH); 7.13-7.52 (8H, m, H Ar); 4.30 (1H, dd, J_{AM} = 12.3, J_{AX} = 6.7, H_A); 3.95 (1H, dd, J_{AM} = 12.3, J_{MX} = 10.7, H_M); 3.52 (1H, dd, J_{AX} = 6.7, J_{MX} = 10.7, H_X); 3.11 (3H, s, NCH_3); 2.37 (3H, s, $ArC\underline{H}_3$); 2.35 (3H, s, $ArC\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm: 148.7 (C-3); 139.5, 136.7, 132.8, 131.6, 130.2, 128.8, 126.4, 123.7 (C Ar); 56.5 (C-5); 51.2 (C-4); 42.3 (NCH_3); 23.7 ($Ar\underline{C}H_3$); 23.5 ($Ar\underline{C}H_3$). Found, %: C 63.06; H 6.11; N 12.33. $C_{18}H_{21}N_3O_2S$. Calculated, %: C 62.95; H 6.16; N 12.23.

4-(4-Chlorophenyl)-3-(4-chlorophenyl)aminosulfonyl-1-methylpyrazoline (3c). Yield 0.72 g (75%). White solid; mp 187-189°C. IR spectrum, ν, cm^{-1}: 3344 (NH), 1606 (C=N), 1336, 1144 (SO_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.41 (1H, br. s, NH); 7.10-7.45 (8H, m, H Ar); 4.28 (1H, dd, J_{AM} = 12.4, J_{AX} = 6.8, H_A); 3.97 (1H, dd, J_{AM} = 12.4, J_{MX} = 11.0, H_M); 3.52 (1H, dd, J_{AX} = 6.8, J_{MX} = 11.0, H_X); 3.10 (3H, s, NCH_3). ^{13}C NMR spectrum, δ, ppm: 146.5 (C-3); 140.5, 137.6, 132.4, 130.2, 129.2, 128.8, 127.9, 122.2 (C Ar); 59.3 (C-5); 51.9 (C-4); 42.9 (NCH_3). Found, %: C 49.92; H 3.97; N 11.05. $C_{16}H_{15}Cl_2N_3O_2S$. Calculated, %: C 50.01; H 3.93; N 10.93.

4-Aryl-3-arylaminosulfonyl-1-methylpyrazoles 4a-c (General Method). A solution of compounds **3a-c** (0.32 g, 1 mmol) and chloranil (0.25 g, 1 mmol) in xylene (10 ml) was refluxed for 24-32 h. Then the reaction mixture was treated with a 5% NaOH solution. The organic layer was separated and repeatedly washed with water. It was dried over anhydrous Na_2SO_4, and the solvent was removed on a rotary evaporator. The resultant solid was purified by recrystallization from 2-PrOH.

1-Methyl-4-phenyl-3-phenylaminosulfonylpyrazole (4a). Yield 0.20 g (65%). White solid; mp 155-157°C. IR spectrum, ν, cm^{-1}: 3340 (NH), 1623 (C=C), 1583 (C=N), 1333, 1140 (SO_2). ^1H NMR spectrum, δ, ppm: 8.35 (1H, br. s, NH); 6.98-7.35 (11H, m, H-5, H Ph); 3.27 (3H, s, NCH_3). ^{13}C NMR spectrum, δ, ppm: 149.5 (C-3); 138.6 (C-5); 137.4 (C-4); 138.2, 136.8, 132.5, 131.8, 129.3, 128.2, 126.4, 125.8 (C Ph); 42.8 (NCH_3). Found, %: C 61.45; H 4.87; N 13.52. $C_{16}H_{15}N_3O_2S$. Calculated, %: C 61.32; H 4.82; N 13.41.

1-Methyl-4-(4-methylphenyl)-3-(4-methylphenyl)aminosulfonylpyrazole (4b). Yield 0.22 g (67%). White solid;.mp 174-176°C. IR spectrum, ν, cm^{-1}: 3340 (NH), 1623 (C=C), 1583 (C=N), 1333, 1140 (SO_2). ^1H NMR spectrum, δ, ppm: 8.32 (1H, br. s, NH); 6.92-7.32 (9H, m, H-5, H Ar); 3.24 (3H, s, NCH_3); 2.35 (3H, s, $ArC\underline{H}_3$); 2.32 (3H, s, $ArC\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm: 149.8 (C-3); 138.1 (C-5); 136.8 (C-4); 137.3, 135.6, 132.2, 131.5, 129.8, 129.1, 128.3, 125.4 (C Ar); 42.5 (NCH_3); 23.9 ($Ar\underline{C}H_3$), 23.7 ($Ar\underline{C}H_3$). Found, %: C 63.25; H 5.66; N 12.40. $C_{18}H_{19}N_3O_2S$. Calculated, %: C 63.32; H 5.61; N 12.31.

4-(4-Chlorophenyl)-3-(4-chlorophenyl)aminosulfonyl-1-methylpyrazole (4c). Yield 0.25 g (68 %). White solid; mp 201-203°C. IR spectrum, ν, cm^{-1}: 3347 (NH), 1625 (C=C), 1603 (C=N), 1337, 1145 (SO_2). ^1H NMR spectrum, δ, ppm: 8.38 (1H, br. s, NH); 7.04-7.39 (9H, m, H-5, H Ar); 3.24 (3H, s, NCH_3). ^{13}C NMR spectrum, δ, ppm: 148.7 (C-3); 139.6 (C-5); 138.8 (C-4); 138.7, 136.2, 132.8, 131.3, 129.5, 128.4, 127.5, 125.6 (C Ar); 43.0 (NCH_3). Found, %: C 50.34; H 3.38; N 11.06. $C_{16}H_{13}Cl_2N_3O_2S$. Calculated, %: C 50.27; H 3.43; N 10.99.

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