Ultrasonicated synthesis of some potent antimicrobial aryl sulphonamides

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Nine *N*-(2,4-difluorophenyl) substituted benzene sulphonamides have been synthesized by ultrasonication method within short reaction time having more than 90% yield. These sulphonamides have been analyzed by spectral and analytical techniques. The higher yields of sulphonamides have been found to be in case of ultrasonication process as compared to microwave and conventional heating methods. The antimicrobial activities of these sulphonamides have been evaluated using Bauer-Kirby disc diffusion method by means of measurement of mm of zone of inhibition.

**Keywords**: Aryl sulphonamides, ultrasonication, IR and NMR spectra, antimicrobial activity

Synthesis employing ultrasonication has recently received much attention from the organic chemistry community1. The main benefits of this method include shorter reaction times and higher yields than conventional processes. Ultrasound irradiation techniques were employed for the preparation of numerous organic compounds including carbonyls2, heterocycles3, carbohydrates4, nanomaterials5, sex hormones6 and polymers7. Sulphonamide synthetic methodology has used such solvents and catalysts   
as methanol2, ionic liquids8, acids9, bases10, N-bromosuccinamide (NBS) (Ref. 9), dimethylformamide (DMF) (Ref. 9), and silanes9. Sulphonamides are important biologically active materials with antibacterial11, antitumor12, anti-malarial13, and anti-HIV (Ref. 14) properties. Sulphonamides are further used as important precursors for bio-potent carbon building blocks15, coordination complexes16, organo-catalysts17, catalysts for water oxidation18, cyclization19, and as protecting groups20.

We now report for the first time the ultrasonicated synthesis of some novel *N*-(2,4-difluorophenyl) substituted benzenesulphonamides. This was done by the potassium phthalate catalyzed ultrasound-assisted condensation of substituted benzene sulphonyl chlorides with 2,4-difluoroaniline for studying antimicrobial activities.

**Results and Discussion**

In our research laboratory, the authors attempt to synthesis some aryl sulphonamides using ultrasonication method by potassium phthalate catalysed condensation of substituted benzene sulphonyl chlorides and 2,4-difluoroaniline in various solvent medium. Our preparative results on the new sulphonamides are presented in Table I and Table II. Generally, we observed that the sulphonyl chlorides bearing electron-donating groups gave higher yields than those with electron-withdrawing substituents. We found that ethanol was the best solvent (Table III). We studied the synthesis of these sulphonamides in (i) conventional heating, (ii) ultrasonication, and (iii) solvent-free microwave methods. Our studies were not all-encompassing; we simply compared some standard procedures that would commonly be used in the synthetic laboratory (see Experimental Section). We found that the ultrasonication process gave higher yields (Table IV).

**Antimicrobial activities**

**Antibacterial activities**

The antimicrobial activities of these sulphonamides were evaluated by Bauer-Kirby21 disc diffusion method. The measured antibacterial activities were determined by measurement of zone of inhibition22-24 of the synthesised compounds and are presented in Table V.

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| Table I — The yield and analytical data for substituted *N*-(2, 4-difluorophenyl)benzene sulphonamides | | | | | | | | | |
| Compd | X | Mol. Formula | Mol. Wt. | m.p. (°C) | Yield  (%) | Time (min) | Micro analysis (%) | | |
|  |  |  |  |  |  |  | C (Calcd) | H (Calcd) | N (Calcd) |
| **1** | H | C12H9F2NO2S | 269 | 163-165 | 94 | 12 | 53.58 (53.53) | 3.32 (3.37) | 5.18 (5.20) |
| **2** | 4-Br | C12H8BrF2NO2S | 348 | 184-186 | 93 | 12.5 | 41.42 (41.40) | 2.30 (2.32) | 3.94 (4.02) |
| **3** | 4-Cl | C12H8ClF2NO2S | 303 | 189-191 | 93 | 12 | 47.48 (47.46) | 2.68 (2.66) | 4.60 (4.61) |
| **4** | 2-F | C12H8ClF3NO2S | 287 | 167-169 | 91 | 13 | 50.21 (50.18) | 2.79 (2.81) | 4.82 (4.88) |
| **5** | 4-F | C12H8ClF3NO2S | 287 | 171-173 | 92 | 12 | 50.20 (50.18) | 2.78 (2.81) | 4.86 (4.88) |
| **6** | 4-OCH3 | C13H11F2NO3S | 299 | 182-185 | 95 | 14 | 52.19 (52.17) | 3.68 (3.70) | 4.62 (4.68) |
| **7** | 4-CH3 | C13H11F2NO2S | 283 | 172-174 | 93 | 13.5 | 55.17 (50.18) | 3.84 (2.81) | 4.86 (4.88) |
| **8** | 2-NO2 | C12H8F2N2O4S | 314 | 176-179 | 91 | 15 | 45.88 (45.86) | 2.52 (2.57) | 8.89 (8.91) |
| **9** | 4-NO2 | C12H8F2N2O4S | 314 | 180-182 | 91 | 15 | 45.85 (45.86) | 2.54 (2.57) | 8.88 (8.91) |

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| Table II — Infrared vibrations (ν, cm−1), 1H and 13C NMR chemical shifts (δ, ppm) and mass spectral fragmentation (*m/z*) | | | | | | | | | | |
| Compd | X | IR (ν, cm−1) | | | 1H NMR (δ, ppm) | | | 13C NMR (δ, ppm) | | Mass (*m/z*) |
| NH | SO*sym* | SO*asym* | NH | Ar-H | X | Ar-C | X |  |
| **1** | H | 3265 | 1334 | 1159 | 6.973 | 6.683-7.474 | − | 104.27-161.87 | − | 269[M+],271[M2+], 273 [M4+] |
| **2** | 4-Br | 3240 | 1346 | 1170 | 7.185 | 6.625-7.025 | − |  | − | 348[M+],350[M2+],352[M4+], 354[M6+] |
| **3** | 4-Cl | 3240 | 1346 | 1168 | 6.804 | 6.523-6.967 | − | 111.23-159.94 | − | 303[M+], 305[M2+], 307[M4+], 309[M6+] |
| **4** | 2-F | 3259 | 1345 | 1144 | 6.955 | 6.419-6.907 | − | 113.25-161.29 | − | 287[M+], 289[M2+], 291 [M4+], 293[M6+] |
| **5** | 4-F | 3256 | 1341 | 1160 | 6.855 | 6.371-6.916 | − | 113.03-161.24 | − | 287[M+],289[M2+],291[M4+], 293[M6+] |
| **6** | 4-OCH3 | 3249 | 1335 | 1155 | 6.983 | 6.428-6.954 | 2.813 | 112.38-160.29 | 59.32 | 299[M+], 301[M2+],303 [M4+] |
| **7** | 4-CH3 | 3222 | 1333 | 1142 | 6.986 | 6.201-6.890 | 2.617 | 112.30-160.39 | 27.31 | 283[M+], 285[M2+], 287 [M4+] |
| **8** | 2-NO2 | 3303 | 1351 | 1145 | 7.208 | 6.413-6.971 | − | 115.23-161.29 | − | 314[M+], 316 [M2+], 318 [M4+] |
| **9** | 4-NO2 | 3245 | 1350 | 1143 | 6.992 | 6.491-6.929 | − | 116.02-161.91 | − | 314[M+], 316 [M2+], 318 [M4+]. |

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| Table III — Effect of solvents on the synthesis of sulfonamides | | | | | | | | | | | | | | | |
| Compd | X | Yield (%) in conventional heating with solvents | | | | | | | Yield (%) in ultrasonication with solvents | | | | | | |
| EtOH | MeOH | PrOH | ACN | THF | DX | DCM | EtOH | MeOH | PrOH | ACN | THF | DX | DCM |
| **1** | H | 73 | 79 | 73 | 72 | 71 | 70 | 68 | 94 | 93 | 90 | 92 | 90 | 93 | 94 |
| **2** | 4-Br | 72 | 68 | 67 | 63 | 64 | 60 | 68 | 93 | 90 | 92 | 90 | 90 | 90 | 91 |
| **3** | 4-Cl | 67 | 63 | 65 | 70 | 67 | 63 | 66 | 93 | 92 | 92 | 92 | 92 | 93 | 92 |
| **4** | 2-F | 70 | 70 | 64 | 71 | 47 | 65 | 67 | 91 | 90 | 90 | 90 | 90 | 90 | 90 |
| **5** | 4-F | 61 | 70 | 62 | 65 | 70 | 68 | 66 | 92 | 90 | 90 | 90 | 90 | 90 | 91 |
| **6** | 4-OCH3 | 76 | 78 | 74 | 77 | 74 | 73 | 70 | 95 | 94 | 93 | 94 | 95 | 94 | 94 |
| **7** | 4-CH3 | 73 | 76 | 72 | 74 | 71 | 70 | 66 | 93 | 92 | 92 | 93 | 94 | 92 | 93 |
| **8** | 2-NO2 | 55 | 60 | 66 | 63 | 64 | 58 | 57 | 91 | 90 | 90 | 90 | 90 | 90 | 90 |
| **9** | 4-NO2 | 42 | 65 | 63 | 61 | 61 | 58 | 59 | 91 | 90 | 90 | 90 | 90 | 90 | 90 |
| EtOH: Ethanol; MeOH: Methanol; PrOH: Propanol; ACN: Acetonitrile; THF: Tetrahydrofuron; DX: Dioxane; DCM: Dichloromethane; Conventional heating done at reflux. | | | | | | | | | | | | | | | |

The majority of the sulphonamides have shown significant antibacterial activity compared to the standard ampicillin. Sulphonamides with 4-NO2,   
4-CH3,2-F and 2-NO2 substituents have shown satisfactory antibacterial activity and the other substituted compounds have no antibacterial activity against *Micrococcus luteus.* The *N*-(2,4-difluorophenyl) substituted phenyl sulphonamides with 4-F, 2-NO2, 2-F and 4-CH3 have shown satisfactory antibacterial and the other substituted compounds have no antibacterial activity against *Streptococcus aureus.* The synthesized-sulfonamide possesses 4-Br, 2-F, 4-F, 4-OCH3, 4-CH3,  
2-NO2 and 4-NO2 substituent shows satisfactory antibacterial activity, the other substituted compounds have no antibacterial activity against *Escherichia coli*. The sulphonamides having H, 2-F, 4-OCH3, 4-CH3,   
2-NO2 and 4-NO2 substituents have shown satisfactory antibacterial activity, against *Pseudomonas aeruginosa*.

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| Table IV — Comparative yields (%) of sulphonamides under different conditions | | | | | | | |
| Compd | X | Conventional heating | | Ultrasonication | | Microwave irradiation | |
| Time (h) | Yield (%) | Time (min) | Yield (%) | Time (min) | Yield (%) |
| **1** | H | 6 | 73 | 12 | 94 | 3 | 62 |
| **2** | 4-Br | 6 | 72 | 14 | 93 | 3.5 | 61 |
| **3** | 4-Cl | 6 | 67 | 13 | 93 | 4 | 61 |
| **4** | 2-F | 6 | 70 | 12 | 91 | 4.5 | 21 |
| **5** | 4-F | 6 | 61 | 14 | 92 | 4 | 23 |
| **6** | 4-OCH3 | 6 | 76 | 11 | 95 | 3 | 64 |
| **7** | 4-CH3 | 6 | 73 | 13 | 93 | 4 | 62 |
| **8** | 2-NO2 | 6 | 55 | 15 | 91 | 6 | 57 |
| **9** | 4-NO2 | 6 | 42 | 15 | 91 | 5 | 43 |

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| Table V — Antibacterial activities of *N*-(2,4-difluorophenyl) substituted phenyl sulphonamides | | | | | |
| Compd | X | Zone of inhibition (mm) | | | |
| Gram-positive | | Gram-negative | |
| *M. luteus* | *S. aureus* | *E. coli* | *P. aeruginosa* |
| **1** | H | − | − | − | 6 |
| **2** | 4-Br | − | − | 6 | − |
| **3** | 4-Cl | − | − | − | − |
| **4** | 2-F | 6 | 7 | 7 | 7 |
| **5** | 4-F | − | 8 | 7 | − |
| **6** | 4-OCH3 | − | − | 7 | 6 |
| **7** | 4-CH3 | 8 | 6 | 7 | 8 |
| **8** | 2-NO2 | 6 | 8 | 6 | 7 |
| **9** | 4-NO2 | 7 | − | 6 | 7 |
| Standard | Ampicillin | 11 | 12 | 12 | 13 |
| Control | DMSO | − | − | − | − |
| −Signifies no inhibition | | | | | |

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| Table VI — Antifungal activities of *N*-(2,4-difluorophenyl)substituted benzene sulphonamides | | | |
| Compd | X | Zone of inhibition (mm) | |
| *Aspergillus niger* | *Trichoderma viride* |
| **1** | H | 8 | 12 |
| **2** | 4-Br | 8 | 11 |
| **3** | 4-Cl | 9 | 10 |
| **4** | 2-F | − | 9 |
| **5** | 4-F | 7 | 12 |
| **6** | 4-OCH3 | 8 | − |
| **7** | 4-CH3 | − | 7 |
| **8** | 2-NO2 | 8 | 8 |
| **9** | 4-NO2 | 9 | − |
| Standard | Miconazole | 13 | 14 |
| Control | DMSO | − | − |
| −Signifies no inhibition. | | | |

The observed antifungal activities of the novel sulphonamides have been tabulated in Table VI.  
Most of the sulphonamides displayed substantial antifungal activity compared to the standard miconazole. The *N*-(2,4-difluorophenyl)substituted benzene sulphonamides with parent, 4-Br, 4-Cl, 4-OCH3, 2-NO2 and 4-NO2 substituents have shown good antifungal activity and the compounds with 4-F substituent have shown satisfactory antifungal activity and the other substituted compounds no antifungal activity against *Aspergillus niger.* The *N*-(2,4-difluorophenyl) substituted benzene sulfonamide compounds with Parent, 4-Br, 4-Cl, 2-F and 4-F substituents have shown good antifungal activity and the 4-CH3 and 2-NO2 substituents have shown satisfactory antifungal activity and the other substituted compounds no antifungal activity against *Trichodermaviride*. These initial results are promising and point the way to future studies embracing structure-activity relationships in a larger set of compounds.

**Experimental Section**

Chemicals used in this work are AnalaR grade   
and purchased from E-Merck and Sigma-Aldrich Chemical companies. The CITIZEN Ultrasonicator, 120W, 40Hz 230V Ac was used for the reaction. Guna make melting point equipment was used for finding the melting points of sulphonamides which are uncorrected. The AVATAR-330 FT-IR spectrophotometer (Thermo Nicolet) was employed for recording the infrared spectra in KBr pellet. The 1H and 13C NMR chemical shifts (δ, ppm) of all sulphonamides were measured in Bruker AV 400 spectrometer using CDCl3 as a solvent and TMS as standard. The micro analysis has been performed in VARIOMICRO V2.2.0 CHN analyzer. The mass spectra of all sulphonamides were recorded in SHIMADZU GC-MS2010 spectrometer using electron impact techniques.

**Typical procedure of synthesis of N-(2,4-difluorophenyl)benzenesulphonamides**

Substituted benzenesulfonyl chlorides (1 mmol), 2,4-difluoroaniline (1 mmol) and 0.5mL of potassium phthalate and 10 mL of ethyl alcohol were taken in 50 mL stoppered flask and mixed thoroughly. This mixture was subjected to ultrasonication for 12-15 minutes in an ultrasonicator at RT (Scheme I). During the reaction, the formation of hydrochloride was neutralized by adding 0.1 mg of potassium carbonate. The ending of the reaction was tracked by Thin Layer Chromatogram. The resulting product was washed with *n*-hexane and separated the catalyst using methanol by filtration and dried to obtain the solid products of substituted *N*-(2, 4-difluorophenyl)benzene sulphonamides(**1-9**). The complete analytical and spectroscopic data of all synthesized substituted   
*N*-(2, 4-difluorophenyl)benzene sulphonamides were summarized in Table I and Table II.

Scheme I.tif

Scheme I — Synthesis of *N*-(2,4-difluorophenyl)benzenesulfonamides

**Measurement of antibacterial activity**

Antibacterial activities of all synthesized sulphonamides were evaluated by the well-known Bauer-Kirby disc diffusion method21. We chose Gram-positive bacterial strains, such as *Micrococcus luteus* and *Staphylococcus aureus;* and we used Gram-negative bacterial strains such as *E. coli and P. aeruginosa*. Ampicillin served as standard and the solvent was dimethylsulfoxide.

**Measurement of antifungal activity**

Antifungal activities of the sulphonamides were determined by the Bauer-Kirby disc diffusion method21. The test organisms were subcultured   
using potato dextrose agar medium. We chose the two fungal stains *Aspergillus niger* and *Trichoderma viride.* Miconazole was used as a standard drug and dimethylsulphoxide as a solvent.

**Conclusion**

In conclusion, we have prepared nine novel sulphonamides and evaluated their biological activities. We compared conventional heating, ultrasonication and solvent-free microwave methods; and we found ultrasonication to be the best. All the new sulphonamides were rigorously characterized. We hope that the ease and convenience of our ultrasonication method will stimulate further research on the preparation of these useful compounds.

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