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Ultrasonicated synthesis of some potent antimicrobial aryl sulphonamides

S Dineshkumar[a], I Muthuvel[a,b], P Mayavel[a,c], R Markanadan[a,d], V Usha[e] & G Thirunarayanan*[a]

[a] Department of Chemistry, Annamalai University, Annamalaiangar 608 002, India
[b] Department of Chemistry, M R Government Arts College, Mannargudi 614 001, India
[c] Department of Chemistry, Government Arts College, Ariyalur 621 713, India
[d] Department of Chemistry, Thiru A Govindasamy Government Arts College, Tindivanam 604 307, India
[e] Department of Chemistry, University College of Engineering Panruti, Panruti 607 106, India
E-mail: drgtnarayanan@gmail.com; thirunarayanan.g.10313@annamalaiuniversity.ac.in

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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 community[1]. 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 carbonyls[2], heterocycles[3], carbohydrates[4], nanomaterials[5], sex hormones[6] and polymers[7]. Sulphonamide synthetic methodology has used such solvents and catalysts as methanol[2], ionic liquids[8], acids[9], bases[10], N-bromosuccinamide (NBS) (Ref. 9), dimethylformamide (DMF) (Ref. 9), and silanes[9]. Sulphonamides are important biologically active materials with antibacterial[11], antitumor[12], anti-malarial[13], and anti-HIV (Ref. 14) properties. Sulphonamides are further used as important precursors for bio-potent carbon building blocks[15], coordination complexes[16], organo-catalysts[17], catalysts for water oxidation[18], cyclization[19], and as protecting groups[20].

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-Kirby[21] disc diffusion method. The measured antibacterial activities were determined by measurement of zone of inhibition[22-24] of the

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	$C_{12}H_9F_2NO_2S$	269	163-165	94	12	53.58 (53.53)	3.32 (3.37)	5.18 (5.20)
2	4-Br	$C_{12}H_8BrF_2NO_2S$	348	184-186	93	12.5	41.42 (41.40)	2.30 (2.32)	3.94 (4.02)
3	4-Cl	$C_{12}H_8ClF_2NO_2S$	303	189-191	93	12	47.48 (47.46)	2.68 (2.66)	4.60 (4.61)
4	2-F	$C_{12}H_8ClF_3NO_2S$	287	167-169	91	13	50.21 (50.18)	2.79 (2.81)	4.82 (4.88)
5	4-F	$C_{12}H_8ClF_3NO_2S$	287	171-173	92	12	50.20 (50.18)	2.78 (2.81)	4.86 (4.88)
6	4-OCH_3	$C_{13}H_{11}F_2NO_3S$	299	182-185	95	14	52.19 (52.17)	3.68 (3.70)	4.62 (4.68)
7	4-CH_3	$C_{13}H_{11}F_2NO_2S$	283	172-174	93	13.5	55.17 (50.18)	3.84 (2.81)	4.86 (4.88)
8	2-NO_2	$C_{12}H_8F_2N_2O_4S$	314	176-179	91	15	45.88 (45.86)	2.52 (2.57)	8.89 (8.91)
9	4-NO_2	$C_{12}H_8F_2N_2O_4S$	314	180-182	91	15	45.85 (45.86)	2.54 (2.57)	8.88 (8.91)

Table II — Infrared vibrations (ν, cm^{-1}), ^1H and ^{13}C NMR chemical shifts (δ, ppm) and mass spectral fragmentation (*m/z*)

Compd	X	IR (ν, cm^{-1})			^1H NMR (δ, ppm)			^{13}C 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[M^{2+}], 273 [M^{4+}]
2	4-Br	3240	1346	1170	7.185	6.625-7.025	–		–	348[M^+],350[M^{2+}],352[M^{4+}], 354[M^{6+}]
3	4-Cl	3240	1346	1168	6.804	6.523-6.967	–	111.23-159.94	–	303[M^+], 305[M^{2+}], 307[M^{4+}], 309[M^{6+}]
4	2-F	3259	1345	1144	6.955	6.419-6.907	–	113.25-161.29	–	287[M^+], 289[M^{2+}], 291 [M^{4+}], 293[M^{6+}]
5	4-F	3256	1341	1160	6.855	6.371-6.916	–	113.03-161.24	–	287[M^+],289[M^{2+}],291[M^{4+}], 293[M^{6+}]
6	4-OCH_3	3249	1335	1155	6.983	6.428-6.954	2.813	112.38-160.29	59.32	299[M^+], 301[M^{2+}],303 [M^{4+}]
7	4-CH_3	3222	1333	1142	6.986	6.201-6.890	2.617	112.30-160.39	27.31	283[M^+], 285[M^{2+}], 287 [M^{4+}]
8	2-NO_2	3303	1351	1145	7.208	6.413-6.971	–	115.23-161.29	–	314[M^+], 316 [M^{2+}], 318 [M^{4+}]
9	4-NO_2	3245	1350	1143	6.992	6.491-6.929	–	116.02-161.91	–	314[M^+], 316 [M^{2+}], 318 [M^{4+}].

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-OCH_3	76	78	74	77	74	73	70	95	94	93	94	95	94	94
7	4-CH_3	73	76	72	74	71	70	66	93	92	92	93	94	92	93
8	2-NO_2	55	60	66	63	64	58	57	91	90	90	90	90	90	90
9	4-NO_2	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.

synthesised compounds and are presented in Table V.

The majority of the sulphonamides have shown significant antibacterial activity compared to the standard ampicillin. Sulphonamides with 4-NO_2, 4-CH_3,2-F and 2-NO_2 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-NO_2, 2-F and 4-CH_3 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-OCH_3, 4-CH_3, 2-NO_2 and 4-NO_2 substituent shows satisfactory

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-OCH_3	6	76	11	95	3	64
7	4-CH_3	6	73	13	93	4	62
8	2-NO_2	6	55	15	91	6	57
9	4-NO_2	6	42	15	91	5	43

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-OCH_3	–	–	7	6
7	4-CH_3	8	6	7	8
8	2-NO_2	6	8	6	7
9	4-NO_2	7	–	6	7
Standard	Ampicillin	11	12	12	13
Control	DMSO	–	–	–	–

–Signifies no inhibition

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-OCH_3	8	–
7	4-CH_3	–	7
8	2-NO_2	8	8
9	4-NO_2	9	–
Standard	Miconazole	13	14
Control	DMSO	–	–

–Signifies no inhibition.

antibacterial activity, the other substituted compounds have no antibacterial activity against *Escherichia coli*. The sulphonamides having H, 2-F, 4-OCH_3, 4-CH_3, 2-NO_2 and 4-NO_2 substituents have shown satisfactory antibacterial activity, against *Pseudomonas aeruginosa*.

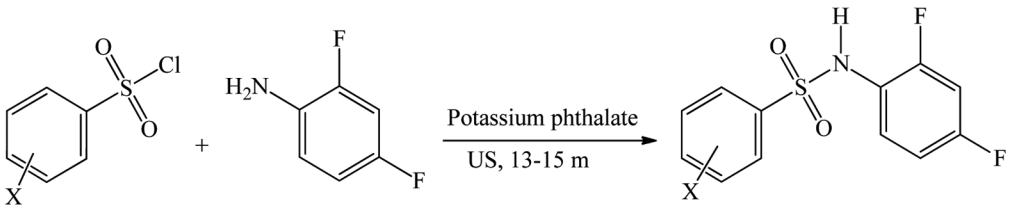
The observed antifungal activities of the novel sulphonamides have been tabulated in Table VI. Most of the sulphonamides displayed substantial antifungal activity compared to the standard miconazole. The *N*-(2,4-difluorophenyl)substituted benzene sulphonamides with parent, 4-Br, 4-Cl, 4-OCH_3, 2-NO_2 and 4-NO_2 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-CH_3 and 2-NO_2 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 ^{1}H and ^{13}C NMR chemical shifts (δ, ppm) of all sulphonamides were measured in Bruker AV 400 spectrometer using $CDCl_3$ 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



Compd	1	2	3	4	5	6	7	8	9
X	H	4-Br	4-Cl	2-F	4-F	4-OCH_3	4-CH_3	2-NO_2	4-NO_2

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

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.

Measurement of antibacterial activity

Antibacterial activities of all synthesized sulphonamides were evaluated by the well-known Bauer-Kirby disc diffusion method[21]. 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 method[21]. 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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