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Green Solid Oxidation of Sulfides to Sulfones Using Oxone and Biological Evaluation

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A 'green' highly selective oxidation of organic sulphides, N-substituted-β-(4-phenyl-2-thiazolyl)thio-alkyl/aryl propionamides (**I**) to the corresponding sulfones (**II**) was developed employing solid-state condition by using oxone. The synthesized compounds were confirmed by using elemental analysis and spectral data. These synthesized compounds were tested for their antibacterial and antifungal activities. None of them were found to possess any promising activity. This oxidation system is found clean, safe, operationally simple and environmentally friendly and meets the needs of contemporary 'Green Chemistry' and is suitable for practical synthesis.

Key Words: Antibacterial activity, Antifungal activity, Oxidation, Oxone.

INTRODUCTION

Sulfone derivatives containing heterocyclic moiety are known for their interesting antibacterial and antifungal bioactivities and have attracted considerable attention in pesticides and medicinal formulations. A large number of reports on their synthesis and biological activities have appeared during the last 3 years[1-8]. To mention few, *p,p'-bis*[[[(2-arylsulfonamido)-1,3,4-oxadiazol-5-yl]methyl]amino]diphenyl sulfones are known for their moderate antifungal and antibacterial activities[9], *p,p'-bis*(5-aryl-1,3,4-oxadiazole-2-yl-methylamino)diphenyl sulfones and *p,p'-bis*(2-aryl-1,3,4-oxadiazol-5-yl)diphenyl sulfones prepared by Meshkatalsadat *et al.*[10,11], exhibit medium inhibitory activity against *Candida albicans* and *Pseudomonas fluores*. Vikani[12] reported *p,p'-bis*(2-substituted-benzalamino/benzoylamino/sulfonamido-1,3,4-thiadiazol-5-yl-ethylamino)diphenyl sulfones displaying good antimicrobial bioactivities against Gram-positive bacteria; *B. mega* and *B. saphilis*, Gram-negative bacteria; *Escherichia coli* and *P. fluores* and fungus; *Aspergillus niger*. All the above works indicated that heterocycles containing sulfones find good applications as antimicrobial agents.

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Along with this, the use of sulfones in organic synthesis has become a classic strategy in the synthesis of demanding and sophisticated complex molecules[13]. From the methodological point of view, sulfones have been employed in the preparation and functionalization of a wide variety of products by stabilizing α-radicals[14], α-anions[15] and acting as cationic synthons[16]. Among the different protocols to prepare sulfones, the oxidation of sulfides has become the most popular and straightforward method in organic synthesis[17].

To date the synthesis of sulfones from sulfides has been widely explored and numerous oxidants have been developed in an effort to achieve a facile, efficient, cheap and selective method. However, most reagents call for carefully controlled reaction condition including quantity of oxidants because of formation of sulfoxides as side products. In order to overcome this problem, Hajipour[18] reported the solid-state oxidation method for the synthesis of sulfones by using oxone (potassium peroxymonosulfate). In his research paper, he explained the 'green' importance of carrying out organic chemical reactions in solid-state conditions.

This data prompted us to prepare sulfones through 'green' solid-state synthesis and evaluate them for their antibacterial and antifungal activities. The final compounds obtained by proposed synthetic method were characterized by using elemental analysis and spectral data.

EXPERIMENTAL

All the melting points and boiling points were determined by open capillary method in liquid paraffin bath. All the solvents were used after distillation. Oxone, aluminum chloride was purchased from S.D. Fine Chemicals, Mumbai. Silica gel G Plates (3 cm × 8 cm) were used for TLC and spots located by iodine vapours in a chamber. Column chromatography was performed on a neutral alumina column (2.5 cm × 45 cm) using appropriate eluent.

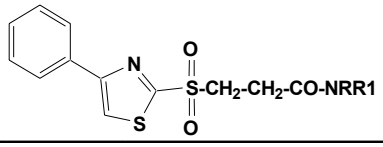
The IR spectra (KBr/nujol) were recorded on Perkin-Elmer FT-IR spectrometer and the values expressed in cm^{-1}. ^1H NMR spectra ($CDCl_3$) were taken on Brooker AC 200 MHz FT using TMS as an internal reference compound.

General method of preparation: A mixture of the appropriate sulfide (1.72 mmol), oxone (4.98 g, 7.92 mmol) and aluminum chloride (0.44 g, 3.4 mmol) was ground with pestle and mortar for 0.5 h and the product was taken up in dichloromethane (3 × 10 mL). The solution was washed with aqueous 20 % sodium bicarbonate ($NaHCO_3$) and water and then the solvent was evaporated. The product was > 95 % pure as found by TLC and ^1H NMR analyses.

The physico-chemical characteristics and spectral data of the newly synthesized compounds (**IIa-f**) are given in Table-1 and Table-2, respectively.

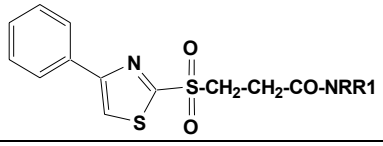
Antibacterial and antifungal activities: The antibacterial and antifungal activities were performed by cup plate method[19,20]. Base layer was obtained by pouring about 10-15 mL of the base layer medium, which was prepared by appropriate known method, into each previously sterilized petri dish and were allowed to attain

TABLE-1
PHYSICO-CHEMICAL DATA OF COMPOUNDS (**IIa-f**)



Compd.	R	R1	m.p. (ºC) / yield (%)	m.f. / (Nature)	Elemental analysis (%): Calcd. (Found)		
					C	H	N
IIa	H	Ph	100-102 (98)	$C_{18}H_{16}N_2O_3S_2$ (White needles)	58.06 (58.00)	4.30 (4.23)	7.53 (7.50)
IIb	H	*p*-C1Ph	115-117 (96)	$C_{18}H_{15}N_2O_3S_2Cl$ (White shining needles)	53.14 (53.00)	3.69 (3.70)	6.89 (6.90)
IIc	H	CH_2Ph	120-122 (96)	$C_{19}H_{18}N_2O_3S_2$ (Offwhite shining needles)	59.07 (59.00)	4.66 (4.70)	7.25 (7.30)
IId	H	*n*-C_3H_7	97-99 (98)	$C_{15}H_{18}N_2O_3S_2$ (Offwhite flakes)	53.25 (53.25)	5.32 (5.35)	8.28 (8.20)
IIe	RR1=Pyrolidine-1-yl		156-158 (95)	$C_{16}H_{18}N_2O_3S_2$ (Offwhite granules)	54.86 (55.00)	5.14 (5.00)	8.00 (8.00)
IIf	RR1=Morpholine-1-yl		166-168 (95)	$C_{16}H_{18}N_2O_4S_2$ (Offwhite granules)	52.46 (52.50)	4.91 (4.85)	7.65 (8.00)

TABLE-2
SPECTRAL DATA OF COMPOUNDS (**IIa-f**)



Compd.	R	R1	IR (KBr, cm^{-1})					1H NMR (ppm) $CDCl_3$
			ν(N=H)	ν(C=O)	ν(C=N)	ν(ArH)	ν(SO_2)	
IIa	H	Ph	3285	1666	1538	705 & 752	1338 & 1152	8.3-7.4 (m, 12, H, 2 × C_6H_5H + NH); 3.80 (t, 2H, $COCH_2$); 2.80 (t, 2H, SO_2-CH_2)
IIb	H	*p*-C1Ph	3260	1668	1548	724 & 750	1340 & 1145	–
IIc	H	CH_2Ph	3320	1654	1542	700 & 740	1338 & 1128	8.21, 7.69-7.4, 6.50 (m, 12H, 2 × C_6-H_5 + 5-H + NH); 4.60 (s, 2H, CH_2, of Benzyl); 3.7 (t, 2H, $COCH_2$); 2.99 (t, 2H, S-CH_2)
IId	H	*n*-C_3H_7	3316	1656	1546	689 & 745	1328 & 1128	–
IIe	RR1=Pyrolidine-1-yl		–	1647	1564	692 & 752	1350 & 1105	–
IIf	RR1=Morpholine-1-yl		–	1646	1565	699 & 748	1345 & 1108	–

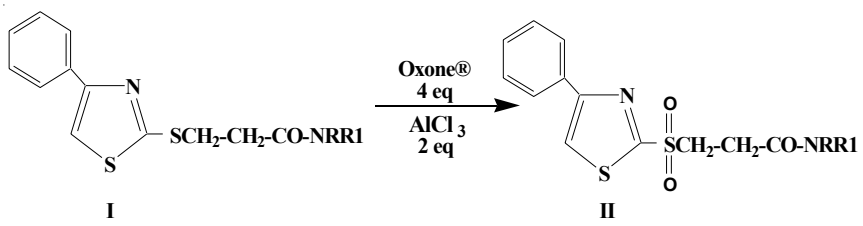
room temperature. The overnight grown subculture was mixed with seed layer medium, which also prepared by appropriate known procedure and about 10-15 mL of this medium was poured over the base layer and again allowed to attain room temperature.

The cups were made by scooping out agar with previously sterilized cork borer. The solutions of test compounds (concentrations 100 and 150 µg/mL) were added in the cups by using pipettes. These plates were subsequently incubated at 37 ºC for 48 h. Inhibitory activity was measured (in mm) as the diameter of the observed inhibition zones for each organism. The tests were repeated to confirm the findings and average of the readings was taken into consideration. The figures obtained are reported as the mean of 3 readings.

Inhibition effects of sulfone derivatives on pathogenic bacteria and fungi were studied *in vitro*. The bacteria, *P. aeuroginose, E. coli* and *S. aureus* and fungi, *C. albicans* and *A. niger* were collected and used in the bactericidal and fungicidal bioassays, respectively. This screening was performed using 100 and 150 µg/mL concentrations of the newly synthesized sulfones (**IIa-f**) using norfloxacin as reference standard for antibacterial activity. Griseofulvin was used as reference standard for antifungal activity and dimethylformamide (DMF) as a control for both the activities.

RESULTS AND DISCUSSION

The purpose of this work was to synthesize various sulfones from the corresponding sulfides with excellent purity, high yields and environmentally friendly way. This was achieved with great success by above described method. When N-substituted-β-(4-phenyl-2-thiazolyl)thio-alkyl/aryl acetamides (**I**) are reacted with oxidant oxone® in pestle and mortar at room temperature, corresponding sulfones (**II**) were obtained in excellent yields (95-98 %) and in high purity (**Scheme-I**).



I **II**

where, (a) R=H; R1=C_6H_5; (b) R=H; R1=$C_6H_4Cl(p)$ (c) R=H; R1=$CH_2C_6H_5$
(d) R=H; R1=*n*-C_3H_7; (e) R R1= Pyrolidine-1-yl (f) R R1= Morpholine-1-yl

Scheme-I

The synthesized compounds were evaluated for both antibacterial and antifungal activities. None of the above compounds showed any promising antibacterial and antifungal activities at 100 and 150 µg/mL concentrations as compared with norfloxacin and griseofulvin, respectively (Tables 3 and 4).

TABLE-3
ANTIBACTERIAL ACTIVITY OF COMPOUNDS (**IIa-f**)

Compd.	R	R1	Zone of inhibition (mm)					
			P. aeuroginose		*S. aureus*		*E. coli*	
			100 µg/mL	150 µg/mL	100 µg/mL	150 µg/mL	100 µg/mL	150 µg/mL
IIa	H	C_6H_5	15	15	28	32	7	12
IIb	H	*p*-C1-C_6H_5	14	16	30	34	7	11
IIc	H	CH_2-C_6H_5	13	14	30	33	8	13
IId	H	*n*-C_3H_7	17	17	28	34	7	13
IIe	RR1= Pyrolidine-1-yl		18	22	31	36	9	14
IIf	RR1= Morpholine-1-yl		18	23	32	37	9	15
Standard	Norfloxacin		18	23	45	50	10	15

TABLE-4
ANTIFUNGAL ACTIVITY OF COMPOUNDS (**IIa-f**)

Compd.	R	R1	Zone of inhibition (mm)			
			C. albicans		*A. niger*	
			100 µg/mL	150 µg/mL	100 µg/mL	150 µg/mL
IIa	H	C_6H_5	23	25	22	24
IIb	H	*p*-C1-C_6H_5	25	27	23	27
IIc	H	CH_2-C_6H_5	26	29	24	28
IId	H	*n*-C_3H_7	28	31	25	27
IIe	RR1= Pyrolidine-1-yl		30	33	27	31
IIf	RR1= Morpholine-1-yl		31	34	31	34
Standard	Griseofulvin		34	38	32	36

Conclusion

As shown, the proposed solid-state synthetic system was found to be a selective method for the oxidation of sulfides to the corresponding sulphones at room temperature. Oxone is proved an excellent Green oxidant promoting the highly chemoselective and fast oxidation of sulfides to sulfones. Different functional groups substituted on sulfur were well tolerated under this environmentally friendly sulfone synthesis protocol. This oxidation system is found easy, rapid and produces the title compounds **II(a-f)** in excellent yields. The structures were verified by spectroscopic data. So, this solid-state oxidation method meets the needs of contemporary 'Green Chemistry' and is suitable for practical synthesis. In the antibacterial and antifungal bioassays, none of the newly synthesized compounds (**IIa-f**) showed any noticeable activity against the said species of the organisms *in vitro*.

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