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Rapid, Economical and Green Solid Oxidation of Sulfides to Sulfones and Their Antimicrobial Evaluation- Part 2

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ABSTRACT

*The sulfones **(IIa-k)** of various 3-(N-substituted carboxamidoethylthio)-(4H)-1, 2, 4-triazoles **(Ia-k)** were synthesized by highly selective oxidation method using oxone®. Through this solid state "Green" oxidation technique, the titled compounds were obtained in good purity and high yields. The structures of the synthesized compounds were confirmed using IR, ^{1}H-NMR spectra and elemental analysis. All the compounds were screened for their antibacterial and antifungal activities. Almost all the compounds showed comparable antibacterial and antifungal activities with that of standards, but none of them found to possess promising these activities. The oxidation system was found clean, safe, operationally simple, and environmentally friendly method. Thus it meets the needs of contemporary "Green Chemistry" and found suitable for practical synthesis.*

Key Words : Green Chemistry, Oxidation, Oxone®, Sulfone, 1, 2, 4-Triazole.

INTRODUCTION

Sulfones containing heterocyclic moieties found to exhibit interesting antibacterial and antifungal bioactivities. Due to this, synthesis of sulfones has attracted considerable attention in pesticides and medicinal formulations [1].

Along with this, the use of sulfones in organic synthesis has become a classic strategy in the synthesis of many of the most demanding and sophisticated complex molecules [2]. From the

methodological point of view, sulfoxides and sulfones have been employed in the preparation and functionalization of a wide variety of products by stabilizing α-radicals [3], α –anions [4] and acting as cationic synthons [5].

Heterocyclic compounds bearing 1, 2, 4-triazole moiety find enormous applications in the field of medicinal chemistry as antibacterial, antifungal, antimicrobial, antiviral, antidepressant, anti-inflammatory agents. A large number of reports on the synthesis and successful pharmacological evaluation of sulfur containing 1, 2, 4-triazoles appeared in the literature [6]. Their corresponding sulfone derivatives also described extensively in the literature with wide commercial applications [7].

Among the different protocols to prepare sulfoxides and sulfones, the oxidation of sulfides has become the most popular and straightforward method in organic synthesis [8]. This is achieved through use of various conventional oxidants. Unfortunately, most of these reagents are not satisfactory for medium- to large-scale synthesis because of the low content of effective oxygen, the formation of environmentally unfavorable co-products, and high cost [9]. In order to overcome this problem, A.R.Hajipour reported the "Green" solid-state oxidation for the synthesis of sulfoxides and sulfones using oxone® (potassium peroxymonosulfate). In the research paper [10], authors explained the importance of carrying out organic chemical reactions in solid state conditions using oxone®.

The chemical composition of oxidizing agent oxone® is $2KHSO_5$. $KHSO_4$. K_2SO_4. The active component potassium monopersulfate ($KHSO_5$, potassium peroxomonosulfate) is a salt from Caro's acid H_2SO_5. The use of oxone® has increased rapidly. Reasons for this are the stability, the simple handling, the non-toxic nature, the versatility of the reagent and low cost [11].

Based on the above literature survey, the authors have published the article on the synthesis and the antimicrobial evaluation of sulfoxides of various 3-(N-substituted carboxamidoethylthio)-(4H)-1, 2, 4-triazoles **(Part-I)** through "Green" solid-state mechanism [12]. In continuation of this, authors also prepared the sulfones **(IIa-k)** of various 3-(N-substituted carboxamidoethylthio)-(4H)-1, 2, 4-triazoles employing the same method. The titled compounds obtained by proposed synthetic method were characterized using elemental analysis and spectral data. These synthesized compounds were also tested for the antibacterial and antifungal activities.

MATERIALS AND METHODS

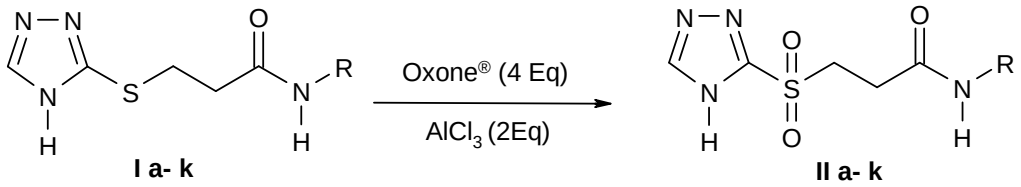
All the melting points and boiling points were determined by open capillary method in liquid paraffin bath. All the solvents were used after distillation. Oxone® and aluminum chloride were purchased from S.D. Fine Chemicals, Mumbai. Silica gel G Plates (3x8cm) were used for TLC and spots located by iodine vapors in a chamber. Column chromatography was performed on a neutral alumina column (2.5x45cm) 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.

Preparation of sulfones: General method

A mixture of the appropriate sulfide **(Ia-k)** (1.72 mmoles), oxone® (4.98 g, 7.92 mmoles) and aluminum chloride ($AlCl_3$) (0.44 g, 3.4 mmoles) was ground with pestle and mortar for 0.5 hr, and the product was taken up in dichloromethane (3 x 10 ml). The solution washed with aqueous 20% sodium bicarbonate ($NaHCO_3$) and water and then the solvent was evaporated. The product sulfone **(IIa-k)** was >95% pure as found by TLC and ^{1}H NMR analysis.

The physicochemical characteristics of newly synthesized compounds **(IIa-k)** are given in **Table 1**.



I a- k **II a- k**

Antibacterial and antifungal activities

The antibacterial and antifungal activities were performed by cup plate method [13,14]. 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 room temperature. The overnight grown subculture was mixed with previously prepared seed layer medium, 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 & 150 µg/ml) were added in the cups using pipettes. These plates were subsequently incubated at 37^{0}C for 48 hours. 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.

Inhibition effects of sulfone derivatives **(IIa-k)** on pathogenic bacteria and fungi were studied *in vitro*. The bacterial species, *P.aeuroginose*, *E.coli* and *S. aureus*, and fungal species, *C. albicans* and *A.niger* were collected and used for the bactericidal and fungicidal bioassays respectively.

This screening was performed using 100 µg/ml and 150 µg/ml concentrations of the newly synthesized sulfones **(IIa-k)** using norfloxacin as a reference standard for antibacterial activity. Griseofulvin was used as a reference standard for antifungal activity and dimethylformamide (DMF) as a control for both the activities. The data of antibacterial and antifungal screening are given in **Table 2** and **Table 3** respectively.

spectral data and elemental analysis of 3-(N-Substituted Carboxamidoethylsulfonyl)-(4H)-1, 2, 4-Triazoles (IIa-k).

(IIa) ***IR (KBr)cm^{-1}***: 3310 (Ar N-H Str.), 3105 (Ar C-H Str), 1665 (C=Ostr.),1565 (2^{0}N-H), 1450 (C-H bend.), 1180 (C-N Str), 1140 & 1338 (S=O_2 Str), 750 (Ar C-H bend.); ***^{1}H NMR (CDCl$_3$)*** : 3.2 (t,2H CH_2), 4.2 (t,2H CH_2), 7.4-8.6 (m,5H-Ar), 8.6 (s,1H CH), 8.6 (s,1H NH)
CHN analysis calculated %: C, 47.14, H, 4.29 N, 20.00 found % C, 47.34, H, 4.09 N, 20.15

(IIb) ***IR (KBr)cm^{-1}***: 3380 (Ar N-H Str.), 3098 (Ar C-H Str),1665 (C=Ostr.),1536 (2^0N-H), 1472 (C-H bend.), 1190 (C-N Str), 1150 & 1340 (S=O_2 Str), 749 (Ar C-H bend.); ***^{1}H NMR (CDCl$_3$)*** : 3.1 (t,2H CH_2), 4.1 (t,2H CH_2), 7.4-8.0 (m,4H-Ar), 8.7 (s,1H CH), 10.6 (s,1H NH) ***CHN analysis*** calculated %: C, 41.97, H, 3.50 N, 17.81 found % C, 42.34, H, 3.01 N, 18.00

(IIc) ***IR (KBr)cm^{-1}***: 3374 (Ar N-H Str.), 3092 (Ar C-H Str),1643 (C=Ostr.),1516 (2^0N-H), 1482 (C-H bend.), 1193 (C-N Str), 1145 & 1326 (S=O_2 Str), 764 (Ar C-H bend.); ***^{1}H NMR (CDCl$_3$)***:3.3 (t,2H CH_2), 4.2 (t,2H CH_2), 7.2-7.8 (m,4H-Ar), 8.6 (s,1H CH), 10.2 (s,1H NH); ***CHN analysis*** calculated %: C, 40.62, H, 3.40 N, 21.55 found % C, 40.02, H, 3.03 N, 22.00

(IId) ***IR (KBr)cm^{-1}***: 3322 (Ar N-H Str.), 3098 (Ar C-H Str),1665 (C=Ostr.),1553 (2^0N-H), 1437 (C-H bend.), 1161(C-N Str), 1145 & 1320 (S=O_2 Str), 773 (Ar C-H bend.); ***^{1}H NMR (CDCl$_3$)***:3.2 (t,2H CH_2), 4.3 (t,2H CH_2), 7.4-7.8 (m,4H-Ar), 8.5 (s,1H CH), 10.3 (s,1H NH); ***CHN analysis*** calculated %: C, 41.97, H, 3.50 N, 17.81 found % C, 42.14, H, 3.47 N, 17.67

(IIe) ***IR (KBr)cm^{-1}***: 3374 (Ar N-H Str.), 3119 (Ar C-H Str),1705 (C=Ostr.),1552 (2^0N-H), 1442 (C-H bend.), 1160 (C-N Str), 1149 & 1337 (S=O_2 Str), 747 (Ar C-H bend.); ***^{1}H NMR (CDCl$_3$)*** : 3.2 (t,2H CH_2), 4.3 (t,2H CH_2), 7.4-7.8 (m,4H-Ar), 8.6 (s,1H CH), 10.3 (s,1H NH) ***CHN analysis*** calculated %: C, 40.62, H, 3.40 N, 21.55 found % C, 41.00, H, 3.49 N, 21.89

(IIf) ***IR (KBr)cm^{-1}***: 3243 (Ar N-H Str.), 3065 (Ar C-H Str),1659 (C=Ostr.),1554 (2^0N-H), 1468 (C-H bend.), 1165 (C-N Str), 1120 & 1347 (S=O_2 Str), 753 (Ar C-H bend.); ***^{1}H NMR (CDCl$_3$)*** :2.6 (s,3H CH_3), 3.2 (t,2H CH_2), 4.1 (s,2H CH_2), 7.3-7.9 (m,4H-Ar), 8.5 (t,1H CH), 10.6 (s,1H NH); ***CHN analysis*** calculated %: C, 48.98, H, 4.76 N, 19.05 found % C, 49.00, H, 5.00 N, 19.00

(IIg) ***IR (KBr)cm^{-1}***: 3298 (Ar N-H Str.), 3086 (Ar C-H Str),1670 (C=Ostr.),1553 (2^0N-H), 1422 (C-H bend.), 1200 (C-N Str), 1140 & 1345 (S=O_2 Str), 800 (Ar C-H bend.); ***^{1}H NMR (CDCl$_3$)*** :2.7 (s,3H CH_3), 3.2 (t,2H CH_2), 4.1 (t,2H CH_2), 7.4-7.8 (m,4H-Ar), 8.6 (s,1H CH), 10.5 (s,1H NH); ***CHN analysis*** calculated %: C, 48.98, H, 4.76 N, 19.05 found % C, 48.99, H, 5.05 N, 18.95

(IIh) ***IR (KBr)cm^{-1}***: 3394 (Ar N-H Str.), 3088 (Ar C-H Str),1626 (C=Ostr.),1518 (2^0N-H), 1439 (C-H bend.), 1185 (C-N Str), 1150 (S=O_2 Str), 755 (Ar C-H bend.); ***^{1}H NMR (CDCl$_3$)*** : 3.2 (t,2H CH_2), 4.2 (t,2H CH_2), 7.5-8.0 (m,4H-Ar), 8.3 (s,1H CH), 10.6 (s,1H NH); ***CHN analysis*** calculated %: C, 40.62, H, 3.40 N, 21.55 found % C, 40.88, H, 3.30 N, 21.78

(IIi) ***IR (KBr)cm^{-1}***: 3348 (Ar N-H Str.), 3090 (Ar C-H Str),1659 (C=Ostr.),1555 (2^0N-H), 1475 (C-H bend.), 1190 (C-N Str), 1138 & 1311 (S=O_2 Str), 789 (Ar C-H bend); ***^{1}H NMR (CDCl$_3$)***:3.2 (t,2H CH_2), 4.1 (s,3H OCH_3), 4.0 (t,2H CH_2), 7.3-7.8 (m,4H-Ar), 8.3 (s,1H CH), 9.8 (s,1H NH); ***CHN analysis*** calculated %: C, 46.45, H, 4.52 N, 18.07 found % C, 46.05, H, 4.80 N, 17.95

(IIj) ***IR (KBr)cm^{-1}***: 3300 (Ar N-H Str.), 3100 (Ar C-H Str),1649 (C=Ostr.),1568 (2^0N-H), 1464 (C-H bend.), 1163 (C-N Str), 1130 & 1346 (S=O_2 Str), 718 (Ar C-H bend.); ***^{1}H NMR (CDCl$_3$)*** :3.0 (t,2H CH_2), 4.1 (t,2H CH_2), 4.6 (d,2H CH_2), 7.4-7.8 (m,5H-Ar), 8.3 (s,1H CH), 10.3(s,1H

NH); ***CHN analysis*** calculated %:C, 48.98, H, 4.76, N, 19.05 found % C, 49.00, H, 5.03, N, 19.05

(**IIk**) ***IR (KBr)cm^{-1}***: 3277 (Ar N-H Str.), 3056 (Ar C-H Str),1676 (C=Ostr.),1527 (2^0N-H), 1450 (C-H bend.), 1173 (C-N Str), 1150 & 1345 (S=O_2 Str), 766 (Ar C-H bend); ***^{1}H NMR (CDCl$_3$)*** :3.3 (t,2H CH_2), 4.2 (t,2H CH_2), 7.4-7.6 (m,4H-Ar), 8.4 (s,1H CH), 10.1(s,1H NH); ***CHN analysis*** calculated %: C, 41.97, H, 3.50, N, 17.81 found % C, 42.00, H, 3.49, N, 18.03

RESULTS AND DISCUSSION

The objectives of this work were to synthesize various sulfones from the corresponding sulfides with great purity, high yields in an environmentally friendly way and screen these synthesized sulfones for the antibacterial and antifungal activities. These objectives were achieved with great success using the said method.

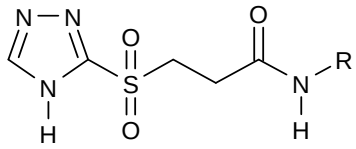
Various 3-(N-substituted carboxamidoethylthio)-(4H)-1, 2, 4-triazoles **(Ia-k)** were reacted with oxidant oxone® and aluminium chloride as a catalyst in pestle and mortar at room temperature, corresponding sulfones **(IIa-k)** were obtained in high yields (95-98 %) and in excellent purity.

The reaction involves a transfer of oxygen radicals towards the sulfide through the formation of peroxo radicals due to the presence of catalyst. It was initially observed that oxone® alone did not initiate the reaction but the peroxo radicals formed causes the reaction to proceed in the desired direction.

Much of the current work in the area of synthesis of sulfones from sulfides focuses on the use of transition metal catalyzed processes [15]. However, a large number of such oxidation reactions often require the use of toxic metal reagents or catalysts. These traditional reagents gave mixture of the corresponding sulfoxides and sulfones and also operating condition was difficult. Consequently, from a “Green Chemistry” standpoint it is very important to develop a “Green” oxidation system for chemical manufacturing. By keeping this view in mind, authors synthesized sulfones from sulfides using oxone®. Oxone® proved as an ideal “Green” oxidant due to its strength and lack of toxic by-products. Thus, this synthetic method ultimately proved to be an environmentally friendly technique.

Sousing this technique, problems associated with the mostly used traditional oxidants are successfully overcome by this simple, effective and efficient “Green” solid state oxidation method employing oxone®. Thus, this solid state synthetic scheme proved extremely useful for the synthesis of sulfones.

Table-1: Physicochemical data of 3-(N-substituted carboxamidoethylsulfonyl)-(4H)-1,2,4-triazoles (IIa-k)



II a- k

Compd.	R	MW	MF	%Yield	M.P.^{0}C
IIa	C_6H_5	280	$C_{11}H_{12}N_4O_3S$	95	130-132
IIb	p-Cl-C_6H_4	314.5	$C_{11}H_{11}ClN_4O_3S$	97	137-139
IIc	p-NO_2-C_6H_4	325	$C_{11}H_{11}N_5O_5S$	96	152-155
IId	m-Cl-C_6H_4	314.5	$C_{11}H_{11}ClN_4O_3S$	96	128-130
IIe	m-NO_2-C_6H_4	325	$C_{11}H_{11}N_5O_5S$	95	136-138
IIf	o-CH_3-C_6H_4	294	$C_{12}H_{14}N_4O_3S$	97	134-137
IIg	p-CH_3-C_6H_4	294	$C_{12}H_{14}N_4O_3S$	96	146-148
IIh	o-NO_2-C_6H_4	325	$C_{11}H_{11}N_5O_3S$	95	195-197
IIi	p-OCH_3-C_6H_4	310	$C_{12}H_{14}N_4O_4S$	97	188-191
IIj	$CH_2C_6H_5$	294	$C_{12}H_{14}N_4O_3S$	96	138-140
IIk	o-Cl-C_6H_4	314.5	$C_{11}H_{11}ClN_4O_3S$	95	130-133

***R**-substitution at amide nitrogen, **MW**- molecular weight, **MF**- molecular formula, **M.P.**- melting point*

Biological Screening

Table 2: Antibacterial activity of compounds (IIa-k)

Comp.	R	Zone of inhibition in millimeter (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	C_6H_5	17	21	31	39	15	21
IIb	p-Cl-C_6H_4	18	23	35	41	17	23
IIc	p-NO_2-C_6H_4	19	22	32	40	19	22
IId	m-Cl-C_6H_4	20	24	34	42	16	24
IIe	m-NO_2-C_6H_4	18	25	33	43	18	22
IIf	o-CH_3-C_6H_4	17	27	36	44	19	23
IIg	p-CH_3-C_6H_4	20	26	37	45	19	24
IIh	o-NO_2-C_6H_4	19	25	35	39	18	25
IIi	p-OCH_3-C_6H_4	18	23	32	41	17	23
IIj	$CH_2C_6H_5$	19	24	33	43	18	21
IIk	o-Cl-C_6H_4	20	25	34	42	19	23
Standard	Norfloxacin	21	28	38	45	20	25

***Comp.** - synthesized compounds, **R**-substitution at amide nitrogen, **P. aeuroginose**- Pseudomonas aeuroginose, **S. aureus**-Staphylococcus aureus, **E. coli**-Escherichia coli.*

As the sulfone derivatives of 1, 2, 4-triazoles compounds possessing good antimicrobial activities[8], the synthesized compounds were evaluated for both antibacterial & antifungal activities. Almost all the compounds **(IIa-k)** exhibited comparable antibacterial and antifungal activities at 100 µg/ml and 150 µg/ml concentrations compared with standard drugs norfloxacin and griseofulvin respectively, but none of them showed promising these activities. However,

from the biological results, it is not possible to draw concrete conclusion about structure activity relationship.

Table 3: Antifungal activity of compounds (IIa-k)

Comp.	R	Zone of inhibition in millimeter (mm)			
		C. albicans		*A. niger*	
		100 µg/ml	150 µg/ml	100 µg/ml	150 µg/ml
IIa	C_6H_5	32	38	27	28
IIb	p-Cl-C_6H_4	33	39	27	30
IIc	p-NO_2-C_6H_4	34	41	29	29
IId	m-Cl-C_6H_4	35	40	28	29
IIe	m-NO_2-C_6H_4	37	42	28	29
IIf	o-CH_3-C_6H_4	38	41	29	31
IIg	p-CH_3-C_6H_4	36	40	30	32
IIh	o-NO_2-C_6H_4	34	40	31	32
IIi	p-OCH_3-C_6H_4	33	39	31	34
IIj	$CH_2C_6H_5$	35	38	30	33
IIk	o-Cl-C_6H_4	36	39	28	33
Standard	Griseofulvin	38	43	31	34

Comp. *- synthesized compounds,* ***R****-substitution at amide nitrogen,* ***C. albicans****- Candida albicans,* ***A. niger****- Aspergillus niger*

CONCLUSION

The present study explained the importance of selective solid state synthesis of sulfides to the corresponding sulfones using “Green” oxidant. Oxidant oxone® proved an ideal candidate due to its stability, the simple handling, the non-toxic nature, the versatility of the reagent and low cost for the highly chemoselective and fast oxidation of sulfides to the sulfones. The synthesized compounds were characterized by spectral data and elemental analysis.

The method has salient features such as faster reaction rates, high yields and environmental friendliness. Different functional groups substituted on sulfur were well tolerated under this environmentally friendly sulfone synthesis protocol.

These sulfone compounds **(IIa-k)** also tested fir its antibacterial and antifungal activities. Almost all the compounds showed comparable the activities.

All in all, “Green” benign procedures described for the synthesis of sulfoxides[12] (**Part 1**) and the sulfones from the sulfides provide a new practical approach for the sulfoxidation and sulphonation respectively because of its simple operation, use of non-toxic and recyclable reagents and the reduction of environmental wastes.

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