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Rapid, economical and green solid oxidation of sulfides to sulfoxides and their antimicrobial evaluation- part 1

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Abstract

*A "green" highly sensitive oxidation of organic sulfides, 3-(N-substituted carboxamido -ethylthio)-(4H)-1, 2, 4-triazoles **(I a-k)** to the corresponding sulfoxides **(II a-k)** was developed employing solid-state condition by using oxone®. The synthesized compounds were confirmed using elemental analysis and spectral data. These 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 and operationally simple, environmentally friendly and meets the needs of contemporary "green chemistry".*

Key Words: 3-(N-substituted carboxamidoethylthio)-(4H)-1, 2, 4-triazole, Oxidation, Oxone®, Sulfoxide.

INTRODUCTION

The growth in the chemistry of organic sulfoxides during last decade was due to their importance as synthetic intermediates for the production of wide range of chemically and biologically active molecules. They often perform major therapeutic functions such as anti-ulcer [1], antibacterial, antifungal, anti-atherosclerotic [2], antihypertensive [3] and cardiotonic agents [4], as well as psychotonics [5] and vasodilators [6]. The oxidation of sulfides to sulfoxides is the most straightforward synthetic route to the latter, and numerous reagents and oxidative procedures are available for this transformation. However, many of them cause overoxidation to the corresponding sulfones. Therefore, control of the reaction conditions, that is, time, temperature and the relative amount of oxidants, plays an important role in avoiding the formation of

oxidation side products. This is often hard to achieve and therefore there is still considerable interest in the development of selective oxidants for this transformation [7-12].

During the literature survey, we found that, A. R. Hajipour [13] reported the "green" solid-state oxidation method for the synthesis of sulfoxides from sulfides using oxone® (potassium peroxymonosulfate).

This available data instigated us to synthesize and perform antibacterial and antifungal evaluation of the sulfoxides of various derivative of 3-(N-substituted carboxamidoethylthio)-(4H)-1, 2, 4-triazoles **(I a-k).** The final compounds, sulfoxides **(II a-k),** were characterized by elemental analysis and spectral data.

RESULTS AND DISCUSSION

The purpose of this work was to synthesize various sulfoxides from the corresponding sulfides with great purity, high yields and environmentally friendly way. This was achieved with good success by the above described method. Much of the current work in the area of synthesis of sulfoxides from sulfides focuses on the use of transition metal catalyzed processes [16-20]. However, a large number of such oxidation reactions often require the use of toxic metal reagents or catalysts. Consequently, from a green chemistry standpoint it is very important to develop a "green" oxidation system for chemical synthesis. Oxone® was proved as an ideal "green" oxidant due to its strength and lack of toxic by-products.

The traditional reagents used in oxidation of sulfides to sulfoxides gave mixture of the corresponding sulfoxides and sulfones and also operating conditions are quiet difficult. These problems associated with the mostly used oxidants were successfully overcome by using this simple, effective and efficient solid-state oxidation method employing oxone®.

The said "green" synthetic method for the solid-state synthesis of sulfoxides from sulfides using oxone® gave high and excellent yields of the products and thus proved extremely useful.

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 when compared with standard drugs norfloxacin and griseofulvin respectively.

MATERIALS AND METHODS

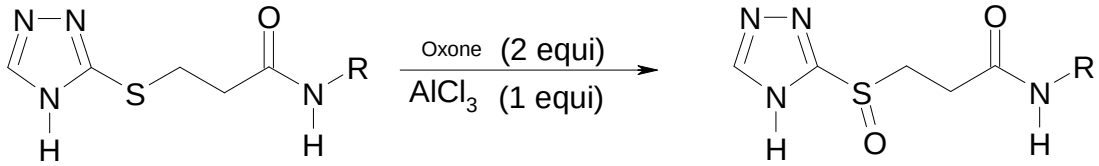
All the melting points and boiling points were determined by open capillary method in liquid paraffin bath and are uncorrected. Oxone® and aluminum chloride were purchased from S.D. Fine Chemicals, Mumbai. Silica gel G Plates (3x8cm) were used for TLC and spots were located by iodine vapors in a chamber. 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.

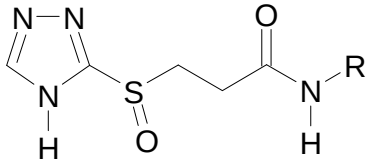
General method of preparation

A mixture of the sulfide (1.72 mmoles), oxone ® (2.4 g, 3.96 mmoles) and aluminum chloride ($AlCl_3$) (0.22 g, 1.7 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 was washed with aqueous 20% sodium bicarbonate ($NaHCO_3$) and water and then the solvent was evaporated. The product obtained were >95% pure as found by TLC and ^1H NMR analysis.

The physicochemical characteristic of newly synthesized compounds (II a-k) is given in **Table 1**.



Ia-k **IIa-k**



II *(a-k)*

Table-1: Physico-chemical data of sulfoxide II (a-k)

Compd.	R	MW	MF	%Yield	m.p.^{0}C
II *a*	C_6H_5	264.30	$C_{11}H_{12}N_4O_2S$	95.1	90-92
II *b*	p-Cl-C_6H_4	298.75	$C_{11}H_{11}ClN_4O_2S$	96.2	77-79
II *c*	p-NO_2-C_6H_4	309.30	$C_{11}H_{11}N_5O_4S$	95.1	122-125
II *d*	m-Cl-C_6H_4	298.75	$C_{11}H_{11}ClN_4O_2S$	95.2	88-90
II *e*	m-NO_2-C_6H_4	309.30	$C_{11}H_{11}N_5O_4S$	95.4	76-78
II *f*	o-CH_3-C_6H_4	278.34	$C_{12}H_{14}N_4O_2S$	95.6	74-77
II *g*	p-CH_3-C_6H_4	278.34	$C_{12}H_{14}N_4O_2S$	95.5	96-98
III *h*	o-NO_2-C_6H_4	309.31	$C_{11}H_{11}N_5O_4S$	95.4	168-170
III *i*	p-OCH_3-C_6H_4	294.33	$C_{12}H_{14}N_4O_3S$	95.3	158-160
II *j*	$CH_2C_6H_5$	278.34	$C_{12}H_{14}N_4O_2S$	95.6	88-90
II *k*	o-Cl-C_6H_4	298.75	$C_{11}H_{11}ClN_4O_2S$	95.8	70-73

***R**-substitution at amido nitrogen, **MW**- molecular weight, **MF**- molecular formula, **m.p.**- melting point*

Antibacterial and Antifungal Activities

The antibacterial and antifungal activities were performed by cup plate method [14-15]. 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 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 & 150 µg/ml) were added in the cups by using pipettes. These plates were subsequently incubated at 37^0C 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. The figures obtained are reported as the mean of three readings.

Inhibition effects of sulfoxide 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 µg/ml and 150 µg/ml concentrations of the newly synthesized sulfoxides **(II a-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. Almost all the compounds **(II a-k)** exhibited moderate inhibitory activity against the said species of organisms but none of them found to have any promising inhibitory activity. The data of antibacterial and antifungal screening are given in **Table 2** and **Table 3** respectively.

Table 2: Antibacterial activity of compounds II (a-k)

Comp	R	Zone of inhibition in millimeter (mm)					
		P.aeuroginosa		***S.aureus***		***E.coli***	
		100 µg/ml	**150 µg/ml**	**100 µg/ml**	**150 µg/ml**	**100 µg/ml**	**150 µg/ml**
II a	C_6H_5	12	14	27	30	09	12
II b	p-Cl-C_6H_4	13	15	29	32	09	11
II c	p-NO_2-C_6H_4	11	13	28	31	10	13
II d	m-Cl-C_6H_4	14	16	27	32	11	13
II e	m-NO_2-C_6H_4	14	15	25	30	10	12
II f	o-CH_3-C_6H_4	14	14	24	25	10	11
II g	p-CH_3-C_6H_4	12	16	23	27	08	13
II h	o-NO_2-C_6H_4	14	14	24	26	07	12
II i	p-OCH_3-C_6H_4	13	15	25	29	09	11
II j	$CH_2C_6H_5$	15	14	26	28	09	13
II k	o-Cl-C_6H_4	13	13	25	30	08	12
Standard	Norfloxacin	20	25	35	40	15	20

Table 3: Antifungal activity of compounds II (a-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
II a	C_6H_5	22	24	21	22
II b	p-Cl-C_6H_4	24	26	22	25
II c	p-NO_2-C_6H_4	25	28	23	26
II d	m-Cl-C_6H_4	27	30	22	24
II e	m-NO_2-C_6H_4	26	22	24	21
II f	o-CH_3-C_6H_4	21	27	20	23
II g	p-CH_3-C_6H_4	23	29	19	24
II h	o-NO_2-C_6H_4	24	23	21	20
II i	p-OCH_3-C_6H_4	26	25	23	21
II j	$CH_2C_6H_5$	27	24	25	22
II k	o-Cl-C_6H_4	25	28	20	25
Standard	Griseofulvin	35	40	33	37

Spectral data and elemental analysis of sulfoxide (II A-K)

(II a) ***IR (KBr)cm^{-1}***: 3303 (Ar N-H Str.), 3096 (Ar C-H Str), 1660 (C=Ostr.),1555 (2^{0}N-H), 1445 (C-H bend.), 1175 (C-N Str), 1140 (S=O Str), 756 (Ar C-H bend.); ***^{1}H NMR (CDCl$_3$)*** : 3.0 (t,2H CH_2), 4.0 (t,2H CH_2), 7.0-7.6 (m,5H-Ar), 8.5 (s,1H CH), 9.6 (s,1H NH); ***CHN analysis*** calculated %: C, 50.00, H, 4.55 N, 21.21 found % C, 50.41, H, 5.07 N, 20.85

(II b) ***IR (KBr)cm^{-1}***: 3374 (Ar N-H Str.), 3078 (Ar C-H Str),1643 (C=Ostr.),1526 (2^{0}N-H), 1462 (C-H bend.), 1180 (C-N Str), 1150 (S=O Str), 758 (Ar C-H bend.); ***^{1}H NMR (CDCl$_3$)*** : 2.9 (t,2H CH_2), 3.9 (t,2H CH_2), 7.2-7.8 (m,4H-Ar), 8.6 (s,1H CH), 10.4 (s,1H NH); ***CHN analysis*** calculated %: C, 44.30, H, 3.70 N, 18.79 found % C, 44.00, H, 3.98 N, 19.07

(II c) ***IR (KBr)cm^{-1}***: 3364 (Ar N-H Str.), 3082 (Ar C-H Str),1633 (C=Ostr.),1506 (2^{0}N-H), 1472 (C-H bend.), 1183 (C-N Str), 1135 (S=O Str), 754 (Ar C-H bend.); ***^{1}H NMR (CDCl$_3$)*** : 3.1 (t,2H CH_2), 4.0 (t,2H CH_2), 7.0-7.8 (m,4H-Ar), 8.5 (s,1H CH), 10.0 (s,1H NH); ***CHN analysis*** calculated %: C, 42.72, H, 3.56 N, 22.65 found % C, 43.10,H, 3.58 N, 23.00

(II d) ***IR (KBr)cm^{-1}***: 3312 (Ar N-H Str.), 3088 (Ar C-H Str),1675 (C=Ostr.),1543 (2^{0}N-H), 1427 (C-H bend.), 1151(C-N Str), 1145 (S=O Str), 783 (Ar C-H bend.); ***^{1}H NMR (CDCl$_3$)*** : 3.0 (t,2H CH_2), 4.1 (t,2H CH_2), 7.2-7.6 (m,4H-Ar), 8.4 (s,1H CH), 10.1 (s,1H NH); ***CHN analysis*** calculated %: C, 44.30, H, 3.70 N, 18.79 found % C, 44.38, H, 3.58 N, 18.80

(II e) ***IR (KBr)cm^{-1}***: 3364 (Ar N-H Str.), 3099 (Ar C-H Str),1695 (C=Ostr.),1542 (2^{0}N-H), 1432 (C-H bend.), 1150 (C-N Str), 1160 (S=O Str), 737 (Ar C-H bend.); ***^{1}H NMR (CDCl$_3$)*** : 3.0 (t,2H CH_2), 4.1 (t,2H CH_2), 7.2-7.4 (m,4H-Ar), 8.5 (s,1H CH), 10.1 (s,1H NH); ***CHN analysis*** calculated %: C, 42.72, H, 3.56 N, 22.65 found % C, 43.11, H, 3.50 N, 22.70

(II f) ***IR (KBr)cm^{-1}***: 3233 (Ar N-H Str.), 3055 (Ar C-H Str),1649 (C=Ostr.),1544 (2^{0}N-H), 1458 (C-H bend.), 1155 (C-N Str), 1170 (S=O Str), 753 (Ar C-H bend.); ***^{1}H NMR (CDCl$_3$)*** : 2.4 (s,3H CH_3), 3.0 (t,2H CH_2), 3.9 (s,2H CH_2), 7.1-7.7 (m,4H-Ar), 8.4(t,1H CH), 10.4 (s,1H NH); ***CHN analysis*** calculated %: C, 51.80, H, 5.04 N, 20.14 found % C, 52.00, H, 5.10 N, 20.20

(II g) ***IR (KBr)cm^{-1}***: 3288 (Ar N-H Str.), 3076 (Ar C-H Str),1660 (C=Ostr.),1543 (2^{0}N-H), 1412 (C-H bend.), 1195 (C-N Str), 1140 (S=O Str), 816 (Ar C-H bend.); ***^{1}H NMR (CDCl$_3$)*** : 2.5 (s,3H CH_3), 3.0 (t,2H CH_2), 3.9 (t,2H CH_2), 7.2-7.4 (m,4H-Ar), 8.5 (s,1H CH), 10.3 (s,1H NH); ***CHN analysis*** calculated %: C, 51.80, H, 5.04 N, 20.14 found % C, 51.93, H, 5.05 N, 20.00

(II h) ***IR (KBr)cm^{-1}***: 3384 (Ar N-H Str.), 3078 (Ar C-H Str),1616 (C=Ostr.),1508 (2^{0}N-H), 1429 (C-H bend.), 1175 (C-N Str), 1150 (S=O Str), 749 (Ar C-H bend.); ***^{1}H NMR (CDCl$_3$)*** : 3.0 (t,2H CH_2), 4.0 (t,2H CH_2), 7.2-7.8 (m,4H-Ar), 8.2 (s,1H CH), 10.4 (s,1H NH); ***CHN analysis*** calculated %: C, 42.72, H, 3.56N, 22.65 found % C, 43.00, H, 4.00 N, 23.00

(II i) ***IR (KBr)cm^{-1}***: 3338 (Ar N-H Str.), 3080 (Ar C-H Str),1649 (C=Ostr.),1545 (2^{0}N-H), 1465 (C-H bend.), 1180 (C-N Str), 1146 (S=O Str), 802 (Ar C-H bend); ***^{1}H NMR (CDCl$_3$)*** : 3.0 (t,2H CH_2), 3.9 (s,3H OCH_3), 3.8 (t,2H CH_2), 7.0-7.5 (m,4H-Ar), 8.2 (s,1H CH), 9.6 (s,1H NH); ***CHN analysis*** calculated %: C, 49.00, H, 4.76 N, 19.05 found % C, 49.01, H, 4.61 N, 20.13

(II j) ***IR (KBr)cm^{-1}***: 3291 (Ar N-H Str.), 3091 (Ar C-H Str),1639 (C=Ostr.),1558 (2^{0}N-H), 1454 (C-H bend.), 1153 (C-N Str), 1160 (S=O Str), 728 (Ar C-H bend.); ***^{1}H NMR (CDCl$_3$)*** : 2.8 (t,2H CH_2), 3.9 (t,2H CH_2), 4.4 (d,2H CH_2), 7.2-7.4 (m,5H-Ar), 8.2 (s,1H CH), 10.1(s,1H NH); ***CHN analysis*** calculated %:C, 51.80,H, 5.04,N,20.14 found % C, 52.00,H, 5.06,N,20.05

(II k) ***IR (KBr)cm^{-1}***: 3267 (Ar N-H Str.), 3046 (Ar C-H Str),1666 (C=Ostr.),1517 (2^{0}N-H), 1440 (C-H bend.), 1163 (C-N Str), 1150 (S=O Str), 756 (Ar C-H bend); ***^{1}H NMR (CDCl$_3$)*** :3.1 (t,2H CH_2), 4.0 (t,2H CH_2), 7.2-7.4 (m,4H-Ar), 8.3 (s,1H CH), 9.9 (s,1H NH); ***CHN analysis*** calculated %: C, 44.30, H, 3.70, N, 18.79 found % C, 44.35, H, 3.85, N, 19.00

CONCLUSION

As shown, the proposed synthetic scheme was found to be a selective method for the oxidation of sulfides to the corresponding sulfoxides at room temperature. Oxone® is proved an excellent Green oxidant promoting highly chemoselective and fast oxidation of sulfide to sulfoxide. Different functional groups substituted on sulfur were well tolerated under this environmentally friendly synthesis protocol. This oxidation system is found clean, safe and operationally simple method which can give sulfoxide products with high yields. So, this solid state oxidation method meets the need of contemporary “green chemistry” and is suitable for practical synthesis. In the antibacterial and antifungal bioassays, none of the newly synthesized compounds **(II a-k)** exhibited any noticeable activity against the said species of the organisms *in vitro*.

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