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Microwave Mediated Synthesis and Anti-Microbial Activity of 5-Alkenyl-1,3,4-Oxathiazol-2-Ones

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ABSTRACT

An easy, efficient, clean and environmentally benign method for the synthesis of various 5-alkenyl-1,3,4-oxathiazol-2-ones from various trimethylsilyl carbonyl amides and chlorocarbonylsulphenyl chloride under microwave irradiation with excellent yields and high purity of the desired products has been developed. The results were compared with conventional methods for their yield and reaction time. The synthesized compounds were characterised by the IR, UV-Visible and ^{1}H-NMR spectral analyses along with elemental analysis. All the investigated compounds have been screened for their antimicrobial activities by agar well diffusion method. All the compounds show moderate to good antimicrobial activity.

Keywords-Environmentally Benign, Microwave Irradiation, Oxathiazolones, Antimicrobial Activity

I. INTRODUCTION

Heterocyclic compounds particularly five heterocyclic have attracted the attention of pharmaceutical community over the years due to their therapeutic values [1-3]. Oxathiazolone derivatives are commonly used in thermal decarbonylation reactions to generate the corresponding derivatives of the short-lived nitrile sulphides. Various substituents can be incorporated at the 5-position including esters, amides and phenols in addition to simple alkyl, alkenyl and aryl groups. The most widely used synthetic approach to 1,3,4-oxathiazol-2-ones involves the treatment of the corresponding carboxamide with chlorocarbonylsulfenyl chloride [4-5]. Many oxathiazolones have been synthesed by using this method. The strong hydrogen bonding network that exists in the amides might not be compensated by the cyclization reaction so that the reaction could be thermodynamically unfavourable. In order to prevent the H-bonding network in the carbonyl amides, trimethylsilyl group (Me_3Si-) could be used to replace the hydrogen. The new starting material, trimethylsilyl carbonyl amides [6] will be expected to have no strong H-bonding and to be very soluble in any organic solvents. However, the literature survey showed that no work has been done on synthesis of oxathiazolones using microwave irradiation and on their anti-microbial activities.

The biological activity of compounds is mainly dependent on their molecular structures. Heterocyclic compounds are acquiring more importance in recent years as these can be found in a large number of compounds which display biological activities [7-9]. Polyfunctionalized heterocyclic compounds containing nitrogen, sulphur, oxygen as heteroatom play important roles in the drug discovery process [10-14]. Analysis of drugs in late development stages or in the market shows that 68% of them are heterocycles [15]. Therefore, it is not surprising that during past decades, compounds bearing heterocyclic nuclei have received much attention

due to their chemotherapeutic value in the development of novel antimicrobials and anthelmintics [16]. Various 1,3,4-oxathiazol-2-ones have been shown to have biological activities [17].The chemistry and applications of various 1,3,4-oxathiazol-2-ones had received little attention until the discovery of the nitrile sulphides [18].

In continuation of our interest on eco-friendly syntheses and antimicrobial activities of different oxathiazolones [19], we now present here a simple and mild protocol of the environmentally benign syntheses and antimicrobial activities of 5-alkenyl-1,3,4-oxathiazol-2-ones from various trimethylsilyl carbonyl amides and chlorocarbonylsulphenyl chloride under microwave irradiation with excellent yields and high purity.

II. EXPERIMENTAL

Materials and Method

The requisite reagents i.e., different amides vis. croton amide, acryl amide, methyl acryl amide and cinnamal amide, used in the synthesis were purchased from Aldrich and used as received without further purification. The requisite trimethylsilyl products of the mentioned amides were prepared in the laboratory as shown in the scheme-1. The used solvents were refluxed with the appropriate drying agent [$CHCl_3$ / P_2O_5, $C_6H_5CH_3$ / Na, EtOEt / CaH_2] and distilled in inert medium prior to use.

The microwave irradiations were performed using a commercial / kitchen microwave oven model BMO: 700T (BPL- make).All irradiation experiments were carried out using a non-rotating annular photochemical reactor. All melting points were determined on a melting point apparatus and are uncorrected. Infrared (KBr) spectra were recorded on a Perkin-Elmer, Model-137 infrared spectrophotometer and UV spectra were determined on a Beckmann-DB spectrophotometer. NMR spectra were recorded on a Brucker Varian-300 MHz NMR spectrometer in $CDCl_3$ with TMS as an internal standard. The chemical shifts are expressed in δ-scale downfield from TMS and proton signals are indicated as *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *m* = multiplet. The TLC was run on silica gel plates using acetone-benzene (1:3) as the irrigant. All compounds were analysed satisfactorily for C, H, S and N using Carl-Ebra 1106 elemental analyser in micro analytical laboratory.

A preliminary antibacterial and antifungal activity have been carried out according to well diffusion method [20]. The synthesized compounds have been studied for their antimicrobial activity in vitro against three tested bacteria (*Staphylococcus aureus, Streptococcus pyogenes* as gram positive bacteria and *Proteus spp*. as gram negative bacteria) and two fungi (*Aspergillus spp. and Candida albican*) were clinical activated and maintained on nutrient agar medium for testing antibacterial activity and sabaroud agar medium for antifungal activity. Ofloxacin was used as a standard drug for antibacterial activity and Ketoconazole was used as a standard drug for antifungal activity.

The assessment of the antibacterial and antifungal activity was based on measurement of the diameter of inhibition zone formed around the well and show that the zone of inhibition increased with the increasing of concentration of the tested compounds as shown in table-3 and table-4 respectively.

Synthesis of Compounds

The general procedure for the microwave mediated synthesis of the investigated compounds follows the scheme-1:

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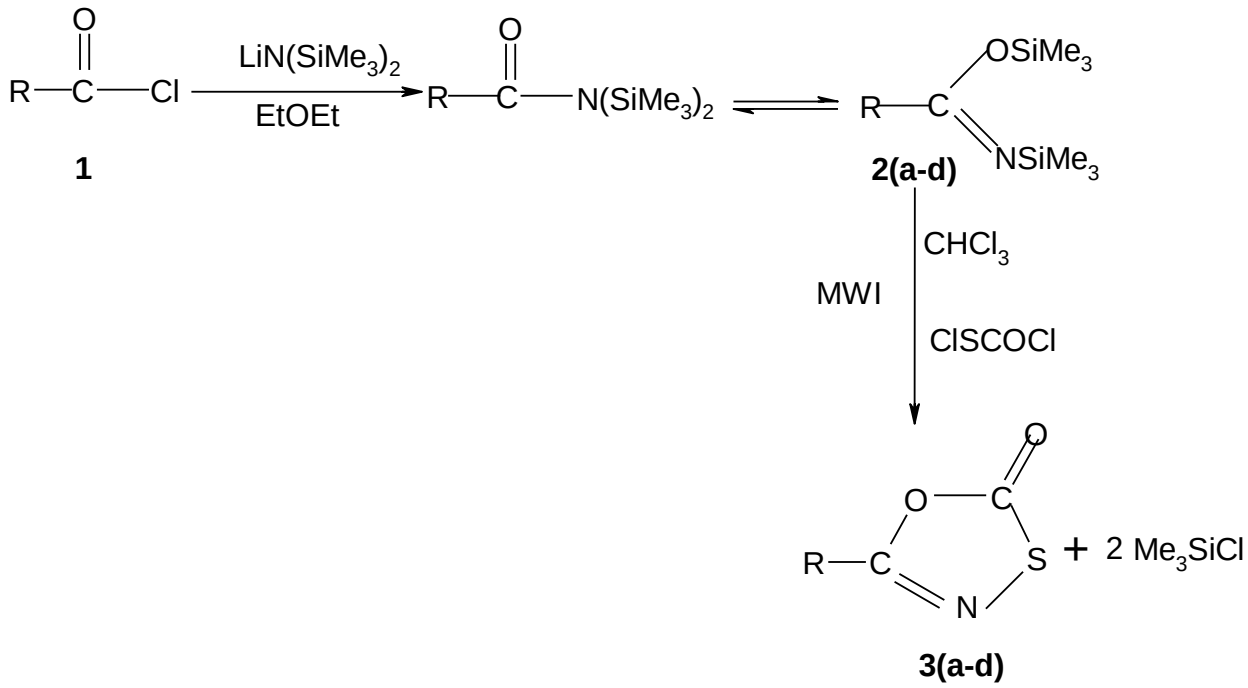


Scheme-1: *Microwave irradiated synthesis of different 5-alkenyl-1,3,4-oxathiazol-2-one* (where for a, R= CH_2=CH-, for b, R= *CH_3-CH=CH-* for c, R= CH_2=C(CH_3)- & for d, R= Ph.CH=CH-)

(a) Synthesis of 5-Vinyl-1,3,4-oxathiazol-2-one(3a): To a solution of trimethylsilyl acryl amide (140 mmol) in dry chloroform (100 mL) at 400 ^{O}C was added ClCOSCl (140 mmol) and the solution refluxed for 12 minutes in a microwave oven. The solvent and unreacted reagent separated by filtration. The residue was chromatographed on silica eluting with petrol/ methylene chloride (4:1) to yield 5-vinyl-1,3,4-oxathiazol-2-one as a yellow oil (52%).

(b) Synthesis of 5-prop-1-enyl-1,3,4-oxathiazol-2-one(3b): To a solution of trimethylsilyl croton amide (240 mmol) in dry chloroform (450 mL) at 200 ^{O}C was added ClCOSCl (230 mmol) and the solution refluxed for 35 minutes in a microwave oven. The solvent was removed under reduced pressure and residue reagent separated by filtration. The residue was chromatographed on silica eluting with petrol/ methylene chloride (4:1) to yield 5-(prop-1-enyl)-1,3,4-oxathiazol-2-one as a white crystalline solid (50%), which was recrystallised from ethanol.

(c) Synthesis of 5-isopropenyl-1,3,4-oxathiazol-2-one(3c): To a solution of trimethylsilyl methyl acryl amide (0.94 mol) in dry chloroform (450 mL) at 240 ^{O}C was added ClCOSCl (0.94 mol) and the solution refluxed for 10 minutes in a microwave oven. The evaporation of the solvent and distillation under reduced pressure yielded 5-isopropenyl-1,3,4-oxathiazol-2-one as a colourless oil which crystallised on cooling (60%).

(d) Synthesis of 5-styryl-1,3,4-oxathiazol-2-one(3d): A mixture of trimethylsilyl cinnamamide (36 mmol) and ClCOSCl (50 mmol) dissolved in dry chloroform (175mL) was refluxed for 15 minutes in a microwave oven. The solvent was removed under pressure yielding a solid, which was chromatographed on silica eluting with

methylene chloride to remove any residual amide. The recrystallisation from cyclohexane produced 5-styryl-1,3,4-oxathaizol-2-one as a white solid (65%).\

Analytical & Spectral Data

Analytical and spectroscopic characterisation of *5-Vinyl-1,3,4-oxathiazol-2-one**(3a):***

Molecular Formula: $C_4H_3NO_2S$ Molecular Mass: 129u

Analytical Data:	%C	%H	%N	%S
Calculated-	27.91	2.23	10.85	24.81
Found-	27.80	2.40	10.90	24.90

Spectral Data: *IR data*: υ_{max} (Film) 1770 (C=O), 1640 (C=C) cm^{-1}.

H NMR data: δ_H ($CDCl_3$): 6.26 (d, 1H, J_{BC} = 17.5Hz, $H^A\underline{H}^BC = CH^C$); 6.22 (d,1H, J_{AC} = 7Hz, H^A); 5.88 (dd, 1H, J_{CA} = 7 Hz, J_{CB} = 17.5Hz, H^C).

^{13}C NMR data: δ_C ($CDCl_3$): 172.6 (C_2); 156.7 (C_5); 122.6 (=CH); 127.4 ($=CH_2$).

Analytical and spectroscopic characterisation of *5-prop-1-enyl-1,3,4-oxathiazol-2-one**(3b):***

Molecular Formula: $C_5H_5NO_2S$ Molecular Mass:143u

Analytical Data:	% C	%H	%N	%S
Calculated-	41.95	3.49	9.79	22.37
Found-	42.05	3.50	9.85	22.40

Spectral Data: *IR data*: υ_{max} (Nujol) 1775 (C=O), 1650 (C=C) cm^{-1}.

H NMR data: δ_H ($CDCl_3$): 6.75 (dq, 1H, J_{BA} = 17Hz, J_{BC} = 7Hz $H^AC=C\underline{H}^BCH_3^C$); 6.02 (dq,1H, J_{AB} = 17Hz, J_{AB} = 7Hz, H^A); 1.94 (dd, 3H, J_{CB} = 7 Hz, J_{CA} = 2Hz, CH_3^C).

^{13}C NMR data: δ_C ($CDCl_3$): 173.2 (C_2); 156.8 (C_5); 141.4 (=CH); 18.6 (CH_3).

Analytical and spectroscopic characterisation of *5-isopropenyl-1,3,4-oxathiazol-2-one**(3c):***

Molecular Formula: $C_5H_5NO_2S$ Molecular Mass: 143u

Analytical Data:	%C	%H	%N	%S
Calculated-	41.95	3.49	9.79	22.37
Found-	42.05	3.50	9.85	22.40

Spectral Data: *IR data*: υ_{max} (Nujol) 1770 (C=O), 1635 (C=C) cm^{-1}.

H NMR data: δ_H ($CDCl_3$): 5.95 (s, 1H, =CH); 5.66 (q,1H, J = 2Hz, =CH); 2.05 (d, 3H, J = 2 Hz, CH_3).

^{13}C NMR data: δ_C ($CDCl_3$): 173.1 (C_2); 158.1 (C_5); 130.7 (=C); 123.8 ($=CH_2$); 17.2 (CH_3).

Analytical and spectroscopic characterisation of *5-styryl-1,3,4-oxathiazol-2-one**(3d):***

Molecular Formula: $C_{10}H_7NO_2S$ Molecular Mass:198u

Analytical Data:	%C	%H	%N	%S
Calculated-	60.60	3.53	7.07	16.16
Found-	60.70	3.60	7.15	16.20

Spectral Data: *IR data*: υ_{max} (Nujol) 1775 (C=O), 1635 (C=C) cm^{-1}.

^{1}H NMR data: δ_H ($CDCl_3$): 7.6 (m, 5H, ArH); 7.44 (d,1H, J = 16Hz, =CH); 6.58 (d,1H, J = 16 Hz, = CH).

^{13}C NMR data: δ_C ($CDCl_3$): 172.7 (C_2); 157.1 (C_5); 133.7 (Ar ring C); 141.3, 112.4 (=CH), 130.1, 128.6, 127.9 (Ar ring CH).

III. DISCUSSION

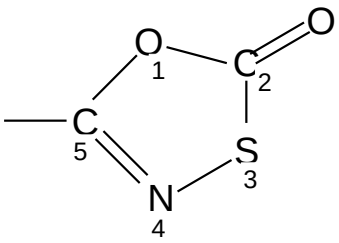
The reaction of the bis(trimethylsilyl)carbonamide (2_{a-d}) with chlorocarbonylsulphenyl chloride under microwave irradiation has been reported here in continuation of various works in our laboratory [19]. In each case no other products were detected and the residual starting materials (amide) was recovered in near very less quantitative yields. All the synthesized compounds (3_{a-d}) were identified and fully characterised by elemental microanalysis, IR, ^{1}H NMR and ^{13}C NMR spectroscopy. This reaction was found to be a better route to synthesize 5- alkenyl-1,3,4-oxathiazol-2-ones than the old one because it was a homogeneous reaction and has taken place in faster way with higher yield compared to the conventional method. In the microwave method homogeneity of reaction mixture was increased by the rotating of reaction platform tray. The confirmation of the results was also checked by the repetition of the synthesis process. Comparative study results obtained by microwave assisted synthesis versus conventional heating method is that some reactions which required 2-24 h. by conventional method, was completed within 10-30 min. by the microwave irradiation technique, yields have been improved from 22-42% to 62-91%(Table-1). The progression of reactions and the purity of the synthesized compounds were checked by TLC.

Table-1: Comparative results of conventional and microwave methods of the compounds under Investigation

Compound	Reaction Time	Yield (%)	Decomposition
	CM [MM (in min.)]	CM(MM)	Temperature(^{0}C)
3a	8h (12)	22 (52)	25
3b	42h (35)	24 (50)	46
3c	18h (10)	18 (60)	29
3d	14h (15)	42 (65)	107

All the products have been identified by all the mentioned spectroscopic and analytical means. It was synthetically easier to use the bis(trimethylsilyl)carbonamides than to use the polyamides $\{R[C(O)NH_2]_n\}$ for this type of reaction to avoid difficulty such as hydrogen bonding and insolubility. The spectroscopic data (except NMR) for the known oxathiazolones related to the 1,3-dipolar cycloaddition reactions of nitriles has not

been well documented. The table-2 summarizes the bond distances and angles in the oxathiazolones related to the nitrile sulphides with dipolarophiles [21]. From **table-2**, the distances of C-O bonds in the investigated oxathiazolone rings are in the range of the standard C-O and S-N bond distances or are slightly longer than the standard single bond. The C-S and S-N bond distances are slightly shorter than the corresponding standard single bonds. The table also clearly indicates that there is no electron delocalization in the heterocycles but there may be a limited conjugation between bonds (e.g. C_5=N_4-S_3-C-) in the oxathiazolone. Therefore, the investigated oxathiazolone heterocycles can be considered as non-aromatic[22].



5-Alkenyl-1,3,4-oxathiazol-2-one

Table-2 Bond distance(Å) and bond angle(^{0}) in the investigated oxathiazolones

compound	3a	3b	3c	3d	literature
O_1-C_2	1.391	1.393	1.387	1.375	1.374
C_2-S_3	1.793	1.768	1.765	1.745	1.798
S_3-N_4	1.702	1.698	1.704	1.687	1.715
N_4-C_5	1.695	1.697	1.716	1.676	1. 672
C_5-O_1	1.289	1.257	1.286	1.298	1.293
S_3-N_4-C_5	107.2	109.3	109.4	109.4	
N_4-C_5-O_1	117.9	118.7	118.3	119.1	
C_5-O_1-C_2	112.3	111.8	112.0	111.5	
O_1-C_2-S_3	106.8	107.2	107.4	107.5	
C_2-S_3-N_4	94.8	94.3	94.1	94.2	

IV. ANTIMICROBIAL ACTIVITY

Most of the newly synthesized compounds were screened for their antimicrobial activity. From the result in **table-3**, compound *3a* showed highly significant activity ($p \leq 0.01$) against all types of bacteria tested in all three concentrations used in comparable to the standard (Ofloxacin). All tested compounds except *3c* showed no to low activity against gram negative bacterium (*Proteus spp*.). At concentration 50µg/mL, compound *3d* showed significant activity($p \leq 0.05$) against gram positive bacterium (*Staphylococcus aureus*) and showed good activity

against gram positive bacterium (Staphylococcus pyogenes). The compounds *3a* and *3c* showed good activity against gram positive bacteria (*Staphylococcus pyogenes* and *Staphylococcus aureus*). The compound *3d* showed good activity against gram negative bacterium (*Proteus spp*.) while the compounds *3a* and *3c* showed no to low activity against gram negative bacterium (*Proteus spp*.). At concentration 120µg/mL, the compound *3c* showed significant activity ($p \leq 0.05$) against gram positive bacteria (*Staphylococcus pyogenes* and *Staphylococcus aureus*). The compound *3a* showed good activity against gram positive bacteria (Staphylococcus pyogenes and Staphylococcus aureus), while compound *3d* showed moderate activity against gram positive bacteria (*Staphylococcus pyogenes* and *Staphylococcus aureus*). The compounds *3a* and *3d* showed good activity against gram negative bacterium (*Proteus spp*.), while compound *3c* showed low activity against gram negative bacterium (*Proteus spp*.).

Table-3 Antibacterial activity of the tested compounds

Compound	Amount	Zone of Inhibition in mm		
		S. aureus	***S. pyogenes***	***Proteus spp.***
3a	2µg/ml	3	4	No activity
	50µg/ml	9	8	4
	120µg/ml	15	13	11
3b	2µg/ml	9	7	5
	50µg/ml	15	12	10
	120µg/ml	25	18	15
3c	2µg/ml	4	3	No activity
	50µg/ml	11	9	3
	120µg/ml	19	14	9
3d	2µg/ml	4	3	No activity
	50µg/ml	13	10	7
	120µg/ml	14	11	8
Ofloxacin	2µg/ml	4	3	6
	50µg/ml	9	8	7
	120µg/ml	18	16	13

From the results in **table-4**, the compound *3b* showed significant activity ($p \leq 0.05$) against all type of fungi tested in all three concentrations used in comparable to the standard (Ketoconazole). At concentration 5µg/mL, all tested compounds except *3b* showed no to low activity against *Aspergillus niger*, while showed low to

moderate activity against *Candida albicans.* At concentration 20µg/mL, compounds *3a* and *3c* showed moderate to good activity against *Aspergillus niger,* while showed low to moderate activity against *Candida albicans.* At concentration 50µg/mL, compound *3c* showed low to moderate activity against *Aspergillus niger,* while compounds*3a* and *3c* showed good activity against *Aspergillus niger.* The compounds *3a* and *3c* showed low to moderate activity against *Candida albicans,* while compound *3d* showed good activity against *Candida albicans.*

Table-4 Antifungal activity of the tested compounds

Compound	Amount	Zone of Inhibition in mm	
		Aspergillus niger	***Candidia albicans***
3a	5µg/ml	5	8
	20µg/ml	10	13
	50µg/ml	15	18
3b	5µg/ml	12	9
	20µg/ml	18	24
	50µg/ml	18	27
3c	5µg/ml	3	5
	20µg/ml	9	6
	50µg/ml	12	15
3d	5µg/ml	4	7
	20µg/ml	5	12
	50µg/ml	15	22
Ketoconazole	5µg/ml	12	10
	20µg/ml	17	25
	50µg/ml	20	30

V. CONCLUSIONS

An easy, efficient, clean and environmentally benign method for the synthesis of four novel 5-alkenyl-1,3,4-oxathiazol-2-ones from various trimethylsilyl carbonyl amides and chlorocarbonylsulphenyl chloride under microwave irradiation with excellent yields and high purity of the desired products has been developed. The results were compared with conventional methods for their yield and reaction time. The synthesized compounds were characterised by the micro-analytical elemental method, IR, UV-Visible and NMR spectral analyses. All the green method synthesized compounds have been screened for their antimicrobial activities by agar well diffusion method. All the compounds show moderate to good antimicrobial activity compared with standard drugs (Ofloxacin for antibacterial activity and Ketoconazole for antifungal activity).

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