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Environmentally Benign Synthesis and Pharmaceutical Evaluation of 5-Substituted-1,3,4-Oxathiazol-2-Ones

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ABSTRACT

A new easy, efficient, clean and environmentally benign method for the synthesis of various 5-substituted-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 chemistry is one of the largest areas of research in organic chemistry and it is growing rapidly. Heterocyclic compounds particularly five and six member heterocyclic have attracted the attention of pharmaceutical community over the years due to their therapeutic values [1-3]. Poly-functionalized heterocyclic containing nitrogen, sulphur, oxygen as heteroatom play important roles in the drug discovery process. 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 antihelmintics [4-5].

Oxathiazolone derivatives are commonly used in thermal decarbonylation reactions to generate the corresponding derivatives of the short-lived nitrile sulphides which may be trapped by 1,3-dipolar cycloaddition reactions to give heterocycles incorporating the C=N-S unit, including isothiazoles and 1,2,4-thiadiazoles in low to high yields depending on the nature of the substituent groups [6-7]. Various substituents can be incorporated at the 5-position including esters, amides and phenols in addition to simple alkyl and aryl groups. Various 1,3,4-oxathiazol-2-ones have been shown to have biological activities [8].The chemistry and applications of various 1,3,4-oxathiazol-2-ones had received little attention until the discovery of the nitrile sulphides [9].

The most widely used synthetic approach to 1,3,4-oxathiazol-2-ones involves the treatment of the corresponding carboxamide with chlorocarbonylsulfenyl chloride [7]. 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 [10] will be expected to have no strong H-bonding and

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to be very soluble in any organic solvents. This is the strategic advantage because a soluble amide may react to much lower temperature as well.

The biological activity of compounds is mainly dependent on their molecular structures [11]. Heterocyclic compounds are acquiring more importance in recent years as these can be found in a large number of compounds which display biological activities [12]. Heterocyclic compounds particularly five and six member heterocyclic have attracted the attention of pharmaceutical community over the years due to their therapeutic values [13]. Polyfunctionalized heterocyclic compounds containing nitrogen, sulphur, oxygen as heteroatom play important roles in the drug discovery process [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].

We now report here the syntheses and antimicrobial activities of different 5-substituted-1,3,4-oxathiazol-2-ones from various trimethylsilyl carbonyl amides and chlorocarbonylsulphenyl chloride under microwave irradiation with excellent yields and high purity in eco-friendly conditions.

II. EXPERIMENTAL

Materials and Method

The requisite reagents {1,4-Cl(O)CC$_6$H$_4$C(O)Cl, MeC[OSiMe$_3$]=NSiMe$_3$, CF$_3$C[OSiMe$_3$]=NSiMe$_3$, ClSC(O)Cl, and ClS(O)Cl} used in the synthesis were purchased from Aldrich and used as received without further purification. The used solvents were refluxed with the appropriate drying agent [CHCl$_3$ / P$_2$O$_5$, C$_6$H$_5$CH$_3$ / Na, EtOEt / CaH$_2$] and distilled in inert medium prior to use.

A preliminary antibacterial and antifungal activity have been carried out according to Well Diffusion Method. 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.

1. Synthesis of 5-alkyl-1,3,4-oxathiazol-2-one

Chlorocarbonylsulfenyl chloride, ClSC(O)Cl, (26 mmol) was added to a mixture of chloroform (48 mL) and *N*, O-bis(trialkylsilyl) acetamide (3a), CH$_3$C[OSiR$_3$]=NSiR$_3$, (12 mmol) under nitrogen to give a clear and slightly yellow solution. The solution was heated at 59°C for 0.5 hours in a microwave oven. The resulting dark red brown solution was subjected to a distillation under vacuum (10^{-3} torr) at room temperature to remove the solvent, the by-product chlorotrialkylsilane and excess ClSC(O)Cl. The product 5-methyl-1,3,4-oxathiazol-2-one (4a) was then sublimed and trapped by a receiver submerged in an ice-water bath, (72%).

IR (cm^{-1}): 1958 (w), 1913 (w), 1823 (s), 1761 (s), 1623 (s), 1430 (m), 1390 (m), 1259 (s), 1044 (m), 997 (m), 920(s), 785 (m), 652 (m).

^{1}H NMR, δ: 2.29 (s).

^{13}C NMR δ: 173.9 (C=O),158.4 (C$_{het}$), 16.1 (CH$_3$).

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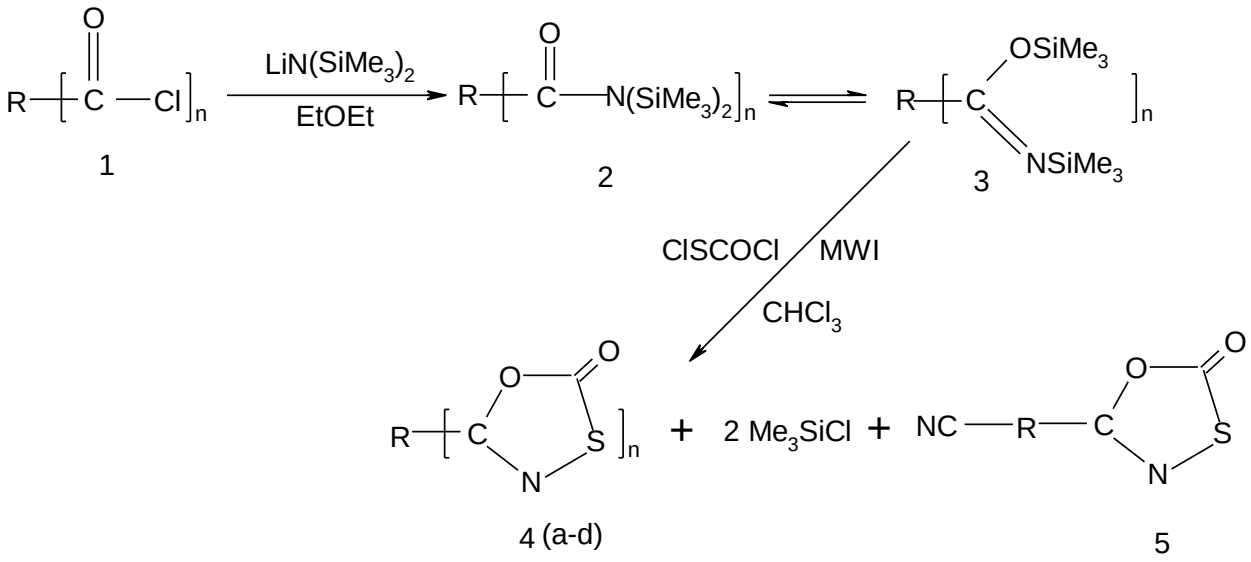
MS [IE, 70eV] m/z (%): 117 (19, M^+), 89 (11, M - CO), 73 (23, CH_3-CNS), 60 (4, COS), 46 (29, NS), 43 (100, CH_3CO), 32 (20, S).

The reaction between the two compounds was monitored by ^1H NMR at 25^0C. A spectrum was taken at time intervals of 20 min.



Scheme-1: *Microwave irradiated synthesis of different 5-substituted-1,3,4-oxathiazol-2-one* (Where for a, n=1, R= Me, for b, n=1, R= *p*-$C_6H_5C_6H_4$ for c & d n=2 R= 1,4-C_6H_4 &4,4'-$C_6H_4C_6H_4$)

2. Synthesis of 5-(4'-Biphenyl)-1,3,4-oxathiazol-2-one

4-Biphenyl-N, O-bis(trimethylsilyl)carbonamide (3b) (3.4 *g*, 9.9 mmol) was dissolved in 70 mL $CHCl_3$ to give a clear yellow solution. Chlorocarbonylsulphenyl chloride (2.8 g, 2 1 mmol) was then added into the solution and the reaction mixture was refluxed for 20 min. and stirred at room temperature for 2 hr. The resulting dark red-orange solution was allowed to stand in a fume hood to remove the excess ClSC(O)Cl and the solvent and an orange-yellow solid (2.8 g) was obtained. The solid was redissolved in $CHCl_3$ and loaded on a column (silica gel, 240400 mesh) and eluted by a solvent mixture of toluene and hexanes (2:l). The desired product 5-(4'-biphenyl)-1,3,4-oxathiazol-2-one (4b) was obtained from the column and recrystallized from toluene as colourless plate-shaped crystals (87%).

IR, (cm^{-1}): 1778 (m), 1731 (s), 1703 (s), 1602 (ms), 1576 (m), 1554 (m), 1519 (m), 1406 (m), 1304 (ms), 1096 (m), 989 (m), 889 (m), 849 (m), 771 (m), 727 (s), 697 (m), 677 (m).

^{1}H NMR, δ: 8.04-8.01 (d, J=7.1Hz, 2H), 7.72-7.69 (d, J = 7.1 Hz, 2H), 7.63-7.61 (d, J = 7.1Hz, 2H), 7.50-7.40 (m, 3H).

^{13}C NMR δ: 173.8 (C=O), 157.2 (C=N), 145.3 (C_{aro}), 139.4 (C_{aro}), 129.0 (C_{aro}), 128.4 (C_{aro}), 127.8 (C_{aro}), 127.6 (C_{aro}), 127.1 (C_{aro}), 124.4 (C_{aro}).

MS [IE, 70eV] m/z (%): 255 (18, M^+), 211 (8, M - CO_2), 179 (100, $C_6H_5C_6H_4$-CN), 153 (16, $C_6H_5C_6H_4$).

Anal. Calcd.: C 65.87, H 3.56, N 5.49; **Found:** C 65.85, H 3.69, N 5.60.

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3. Synthesis of 1,4-bis(1',3',4'-oxathiazol-2'-one-5'-yl)benzene

1,4-Bis[N,O-bis(trimethylsilyl)benzamide (3c)(11mmol) was dissolved in dry $CHCl_3$(85mL) to give a yellowish solution. Chlorocarbonylsulphenyl chloride 50mmol) was added into the solution under argon and heat was immediately evolved. The solution was refluxed for 0.5 hr in a microwave oven with stirring to give a yellow solution over a yellowish-while solid. Filtration of the reaction mixture gave a pale yellow solid which turned pink in colour upon exposure of light for and was identified as 1,4-bis(1',3',4'-oxathiazol-2'-one-5'-yl)benzene (4c)(78%).

IR, (cm^{-1}): 1769(m), 1736(s), 1704(m), 1602(w), 1581(w), 1406(ms), 1314(m), 1291(m), 987(m), 883(w), 856(w), 721(w), 684(m).

MS [IE, 70eV] m/z (%):280 (30.19, M^+), [281 (4.18), 282(3.22)], 236 (3, M-CO_2), 206(100, [COCONS]C_6H_4-CO; [207(10.24), 208 (5.47)]), 178 (24,[COCONS]C_6H_4 or [OCNS] C_6H_4-CO), 162 (10, OC C_6H_4-CNS), 132(64, OC C_6H_4-CO), 130 (56, OC C_6H_4-CN), 104(45, C_6H_4-CO), 102 (29, C_6H_4-CN), 76 (33, C_6H_4).

Anal. Calcd.: C 48.39, H 1.63, N 11.29;

Found: C 36.78, H 1.82, N 11.12.

4. Synthesis of 4,4'-biphenyl-[bis(1",3",4"-oxathiazol-2'-one)]

4,4'-Biphenyl-bis[N,O-bis(trimethylsilyl)carbonamide (3d)(9.8 mmol) was dissolved in $CHCl_3$ (100 mL) to give a clear yellow solution. Chlorocarbonylsulphenyl chloride (44 mmol) was then added into the solution and the reaction mixture was refluxed for 10 min. in a microwave oven and then stirred at room temperature for 12 hr. The resulting orange solution over an orange solid were separated by filtration. Both the solution and the solid (89%) turned to yellow upon exposure to air. The solid was found to be insoluble in any solvent and started to decompose at 185^0C without melting.

IR, (cm^{-1}): 1773(s), 1734(s), 1706(s), 1598(ms), 1547(m), 1398(m), 1303(ms), 1117(w), 1096(m), 985(ms), 884(m), 829(m), 721(m), 681(w).

MS [IE, 70eV] m/z (%):356 (2, M^+), 296 (1, M-COS), 280(19, M-COOS), [207(10.24), 236 (8, $NCC_6H_4C_6H_4CNS$), 206 (100, $NCC_6H_4C_6H_4CO$), 204 (73, $NCC_6H_4C_6H_4CN$), 177(32, $NCC_6H_4C_6H_3$), 151 (36, C_6H_4-C_6H_3), 102(6, CNSC(O)O).

The product appeared to be 4, 4'-biphenyl-[bis(1", 3",4"- oxathiazol-2"-one (4d)

V. RESULTS AND DISCUSSION

A novel synthesis of 5-substinited-1,3,4-oxathiazol-2-ones(4) from the reaction of bis(trimethylsilyl) carbonyl amides (3) with ClSC(O)Cl was discovered. This reaction was found to be a better route to 1,3,4-oxathiazol-2-ones than the old one because it was a homogeneous reaction and could take place at room temperature. Several oxathiazolones (compounds 4(a-d)*)* were synthesized from this reaction. As a result of microwave assisted synthesis, it was observed that the reaction was completed in a short time with higher yields 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

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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 39-66% to 72-89%(Table-1).

The reaction of the bis(trimethylsilyl) carbonamide (3) with chlorocarbonylsulphenyl chloride under microwave irradiation has not been reported before. The first reaction examined was that of N,O-bis(trimethylsilyl)acetamide with ClSC(O)Cl in hot toluene (90- 100°C). Unfortunately, no product was isolated from the reaction mixture for two major reasons: the high reaction temperature and high boiling point of the solvent (b-p. 110°C). Chloroform b.p. 60.9°C) was chosen to replace toluene so that the reaction could be carried out at a lower temperature and the solvent could be easily separated from the product [even with the liquid product 5-methyl-1,3,4-oxathiazol-2-one 4a b.p. 75- 76^0C / 30 torr [17]]. 5-Methyl-1,3,4 oxathiazol-2-one 4a has been synthesized from the reaction of the amide [$RCONH_2$] with ClSC(O)Cl previously [17-18]. The reaction of N,O-bis(trimethylsilyl)acetamide with ClSC(O)Cl in $CHCl_3$ was performed and examined in the mentioned microwave oven.

The reaction of 4-biphenyl-N,O-bis(trimethylsilyl)carbonamide (3c) with ClSC(O)Cl gave the expected product oxathiazolone 4c in 89% yield. The product has been identified by al1 spectroscopic and analytical means. The cycloadduct bis(oxathiazolones) (4c-d) from the reactions of the bisamides (3c and 3d) with ClSC(O)Cl could not be fully characterised because of their insolubility in any solvent which led the difficulty in purifications. The IR and MS spectra of compound 4d gave good evidence for the structure of oxathiazolones and the observation of decomposition at 185-200°C for these two compounds was a good supporting evidence for the conjugated oxathiazolones.

Table-1: Comparative Results of Conventional and Microwave Methods of the Compounds Under Investigation

Compound	Reaction Time	Yield (%)	Decomposition Temperature(^{0}C)
	CM (MM)	CM(MM)	
4a	24h (30)	42 (72)	76
4b	2h (20)	59 (87)	178
4c	2h (30)	39 (78)	198
4d	10h (10)	66 (89)	185

(CM = Conventional method, time in hours; MM = Microwave method, time in minutes)

Based on the results above, it was show that the bis(trimethylsilyl)carbonamides 4 could replace the amides ($RC(O)NH_2$ to react with ClSC(O)Cl to form 5-substituted-1, 3,4-oxathiazol-2-ones (4a-d). 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, or when a low temperature is required for the reaction. From these results and those from other oxathiazolones, it is reasonable to believe that all the rings in oxathiazolones 4a-d should be coplanar and then should be an electron delocalization among the rings in these molecules in solid state.

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VI. ANTIMICROBIAL ACTIVITY

Most of the newly synthesized compounds were screened for their antimicrobial activity. From the result in **table-2**, at concentration 2µg/ml, compound 4c showed highly significant activity ($p \leq 0.01$) against gram positive bacterium (*Staphylococcus aureus),* and showed significant activity ($p \leq 0.05$) against gram positive bacterium (*Streptococcus pyogenes*). Compounds 4a and 4b showed significant activity ($p \leq 0.05$) against gram positive bacteria (*Streptococcus pyogenes* and *Staphylococcus aureus),* while all other tested compounds showed moderate to good activity against gram positive bacteria (*Streptococcus pyogenes* and *Staphylococcus aureus).* All tested compounds except compounds 4c &4d showed no activity against gram negative bacterium (*proteus spp.*).

At concentration 50µg/ml, compound 4c showed significant activity ($p \leq 0.05$) against gram positive bacterium (*Staphylococcus aureus),* and showed good activity against gram positive bacterium (*Streptococcus pyogenes*). Compounds 4a and 4b showed good activity against gram positive bacteria (*Streptococcus pyogenes* and *Staphylococcus aureus),* while compound 4d showed good activity against gram positive bacterium (*Staphylococcus aureus).* Compounds 4a and 4b showed good activity against gram negative bacterium (*Proteus spp*), while compounds 4c and 4d showed no to low activity against gram negative bacterium (*Proteus spp*).

At concentration 120µg/ml, compounds 4a, 4b and 4c showed significant activity ($p \leq 0.05$) against gram positive bacteria (*Staphylococcus aureus* and *Streptococcus pyogenes*). Compound 4d showed moderate activity against gram positive bacteria (*Streptococcus pyogenes* and *Staphylococcus aureus).* Compounds 4a, 4b and 4c showed good activity against gram negative bacterium (*Proteus spp*), while compound 4d showed low activity against gram negative bacterium (*Proteus spp*).

Table-2: Antibacterial activity of the tested compounds

Compound	Amount	Zone of Inhibition in mm		
		S. aureus	***S. pyogenes***	***Proteus spp.***
4a	2µg/ml	5	4	2
	50µg/ml	10	11	8
	120µg/ml	19	18	14
4b	2µg/ml	4	3	6
	50µg/ml	9	8	7
	120µg/ml	18	16	13
4c	2µg/ml	6	5	No activity
	50µg/ml	13	11	2
	120µg/ml	20	18	12
4d	2µg/ml	3	2	No activity
	50µg/ml	9	6	No activity
	120µg/ml	12	9	4
Ofloxacin	2µg/ml	4	3	6
	50µg/ml	9	8	7
	120µg/ml	18	16	13

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From the results in **Table-3**, all the tested compounds 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 20µg/ml, compounds 4a, 4b and 4d showed moderate to good activity against (*Aspergillus niger)*, while showed low to moderate activity against (*Candida albicans*).

At concentration 50µg/ml, compound 4d showed low to moderate activity against (*Aspergillus niger)*, while compounds 4a, 4b and 4d showed good activity against (*Aspergillus niger*). All the compounds showed low to moderate activity against (*Candida albicans*). **Figures** (**1**) and (**2**) demonstrate the antimicrobial activities of tested compounds.

Table-3: Antifungal activity of the tested compounds

Compound	Amount	Zone of Inhibition in mm	
		Aspergillus niger	***Candidia albicans***
4a	5µg/ml	4	5
	20µg/ml	9	8
	50µg/ml	17	14
4b	5µg/ml	5	7
	20µg/ml	10	11
	50µg/ml	15	16
4c	5µg/ml	No activity	2
	20µg/ml	3	7
	50µg/ml	10	11
4d	5µg/ml	3	4
	20µg/ml	8	10
	50µg/ml	15	16
Ketoconazole	5µg/ml	12	10
	20µg/ml	17	25
	50µg/ml	20	30

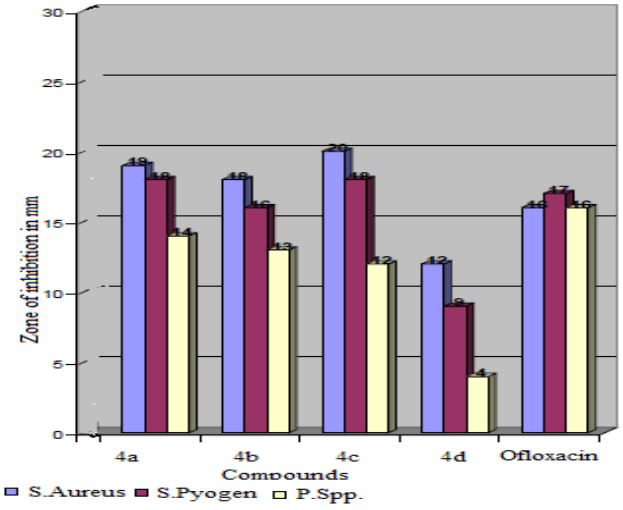

Figure-1: Antibacterial activity of tested compounds at concentration 120 µg/ml on the three types of bacteria

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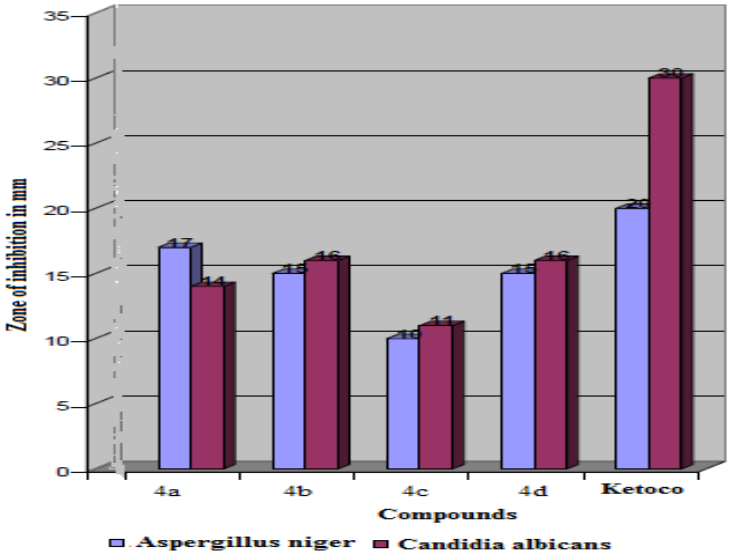

Figure-2: Antifungal activity of tested compounds at concentration 50 µg/ml on the two types of fungi

VII. CONCLUSIONS

A novel synthesis of 5-substinited-1,3,4-0xathiazol-2-ones (41) from the reaction of bis(trimethylsilyl) carbonyl amides (3) with ClSC(O)Cl was discovered. This reaction was found to be a better route to 1,3,4-oxathiazol-2-ones than the old one because it was a homogeneous reaction and could take place at room temperature. Several oxathiazolones (compounds 4a-d*)* were synthesized from this reaction. The preliminary study of antimicrobial activity was done on 3 different strains of bacteria and 2 strains of fungi. The results showed that compounds (4a and 4c) have significant ($p \leq 0.05$) activity compared with standard drugs (Ofloxacin for antibacterial activity and Ketoconazole for antifungal activity), and the other tested compounds have moderate to good activity.

REFERENCES

[1.] A Achson; *An introduction to the chemistry of heterocyclic compounds*, 3rd ed., **2009**, Willy-Intersciences, India.

[2.] D B Shinde, M J Aaglawe, S S Dhule, S S Bahekar, P S Wakte; *J Kor Chem Sty*, **2003**, 47: pp. 133-136

[3.] H Shivganga; *Asian J Research Chem*., **2010**, 3(2): pp.421-427.

[4.] L P Singh, V Chawla, P Chawla, S K Saraf; *Der Pharma. Chemica*, **2010**, 2(4), pp. 206-212.

[5.] V F Priya, K S Girish, K Balakrishna; *Journal of Chemical Sciences*, **2007**, 119(1): pp.41–46.

[6.] K G B Torssell; *Nitrile Oxides, Nitrones, and Nitronates in organic Synthesis*, VCH, Weinheim, **1988**.

[7.] J E Franz, L L Black ; *Tetrahedron Lett.*, **1970**, 138, 1.

[8.] R M Paton, I Stobie, K M Mortier; *Phosphorus Sulfur*, **1983**, 137, 15.

[9.] M M Kremiev, A I Tanenko, and LV Kovd, *Chem Abst.*, **1974**, 81, 3837.

[10.] G Zumach, E Kuhle; *Angew. Chem.. Int. Ed. Engl.*, **1970**, 9, 54.

[11.] Al-Shihry, S Shar; *Sci J Faisal Unv*, **2005**, 16: pp. 77-85.

[12.] V Padmavathi, DRCV Subbaiah, K Mahesh, T R Lakshmi; *Chem Pharm Bull*, **2007**, 55: pp. 1704-1709.

[13.] D B Shinde, M J Aaglawe, S S Dhule, S S Bahekar, P S Wakte; *J Kor Chem Sty*, **2003**, 47: pp. 133-136

IJARSE
ISSN (O) 2319 - 8354
ISSN (P) 2319 - 8346

[14.] A Bazgir, M M Khanaposhtani, A A Sooski; *Bioorg Med Chem Lett*, **2008**, 18: pp. 5800-5803.

[15.] R Dahiya, A Kumar, R Yadav; *Molecules*, **2008**, 13: pp. 956-976.

[16.] K F Ansari, C Lal; *Eur J Med Chem*, **2009**, 44: pp. 2294-2298.

[17.] R K Howe, T A Gruner, L G Cartar, L L Black, J E Franz; *Journal of Organic Chem*, **1978**, 43, 3736.

[18.] E W Colvin; *Silicon in organic Synthesis*, **1981**, Butterworth's, London.