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Comparision study between convenstional method and mircrowave irradiation method to synthesize oxadiazole derivatives

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ABSTRACT

The survey of literature reveals that 1,3,4-oxadiazole moiety possesses a wide range of pharmacological activities such as antimicrobial, antimitotic, analgesic, antilieshmanial, antimycobacterial, antiinflamatory, antiinsecticidal, antitubercular and anti-HIV. Oxadiazole derivatives found to possess certain specific pharmacological activities. By taking the view in the mind we are prepared some oxadiazole derivatives by conventional and microwave irradiation method. In this work we compared the conventional and microwave irradiation methods.

Keywords: Oxadiazole, Conventional, Microwave irradiation method.

INTRODUCTION

- Microwave-assisted organic synthesis is an enabling technology for accelerating drug discovery and development processes.
- Microwave organic synthesis opens up new opportunities to the synthetic chemist in the form of new reaction that are not possible by conventional heating and serve a flexible platform for chemical reaction.
- This review focuses on the advances in the developing of innovative application of microwave mediated synthesis.
- The efficiency of microwave flash-heating chemistry in dramatically reducing reaction times (reduced from days and hours to minutes and seconds) has recently been proven in several different fields of organic chemistry.
- The time saved by using focused microwaves is potentially important in traditional organic synthesis but could be of even greater importance in high-speed combinatorial and medicinal chemistry.

The growing patent literature of recent years demonstrates that the 1,3,4-oxadiazoles are of great practical significance concerned primarily in drug synthesis, production of polymers [1], preparation of dyes [2], as X-rays contrast materials [3], in photography [4], as light screening agents [5], and as scintillators [6]. They also have applications in medicine and agriculture [7].

1, 3, 4-Oxadiazolin-5-ones and 1, 3, 4-oxadiazoline-5-thiones are reported to possess antitubercular [8, 9, 10] antifungal [11], antibacterial [12, 13], antihypertensive [14], analgesic, antipyretic and antiphlogistic properties [15]. The sulfonamide derivatives of 1,3,4-oxadiazole are established not only as bactericides but also as hypoglycemic agents [16].

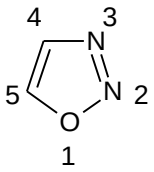
2-amino-5-phenyl-1, 3, 4-oxadiazole and 2-phenyl-1,3,4-oxadiazolin-5-one possess anticonvulsive and paralytic activity, while 2-hydroxyphenyl-1,3,4-oxadiazole are hypnotic and sedative.

CHEMISTRY

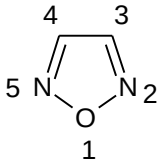
Compounds having a five membered ring containing one oxygen and two nitrogen atoms are called oxadiazoles.

Four types of oxadiazole [17] are known namely 1,2,3-, 1,2,4-, 1,2,5- and 1,3,4-oxadiazoles. Out of these 1,3,4-oxadiazoles are found to be most potent biologically

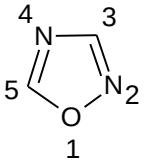
Oxadiazoles [8] are considered to be derived from furan by the replacement of two methine (-CH=) groups by two pyridine type of nitrogens (-N=). There are four isomeric types of oxadiazoles depending on the position of nitogen atoms in the oxadiazole ring and are numbered as



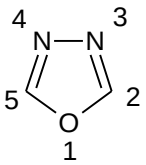
1,2,3-oxadiazole



1,2,5-oxadiazole



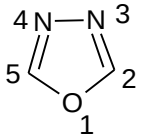
1,2,4-oxadiazole



1,3,4-oxadiazole

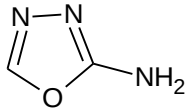
The replacement of two methine (-CH=) groups by two pyridine type of nitrogens (-N=) reduces aromaticity of the resulting oxadiazole ring to such an extent that the oxadiazole ring exhibits character of a conjugated diene.

1,3,4-oxadiazole ring is an aromatic molecule with resonance energy 167.4 kj/mole. The ring is symmetrical and planar with the following structural parameters:



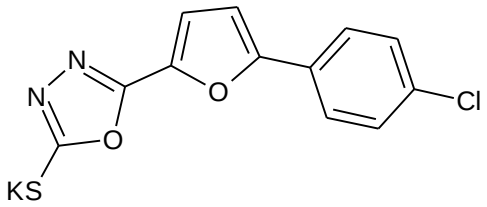
1,3,4-Oxadiazole contains pyridine type nitrogen at position 3 and 4 which cause electron withdrawal from the carbons at positions 2 and 5. Therefore these have low electron density on the nitrogen atoms. Because of very low π-electron density on the carbon atoms the attack of electrophiles preferentially occurs at nitrogen whereas the nucleophiles attack at 2 and 5 carbon atoms.

Ghirian et al., [22] (1974) reported the antimitotic activity of 2-amino1,3,4-oxadiazole(1).



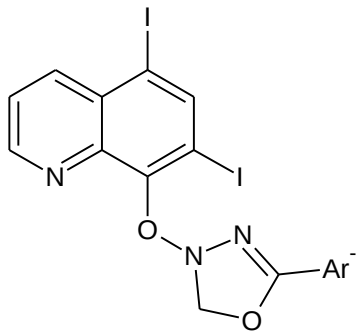
1

Pandey et al., [23] (1977) reported Mannich bases from 5-(2',4',5'- trichlorophenoxymethyl)-1,3,4-oxadiazole-2-thiones as useful fungicides. Potential antifungal agents were found to contain 2-[5-(4-chlorophenyl)-2-furamyl]-5-mercapto-1,3,4-oxadiazole potassium salts (2).



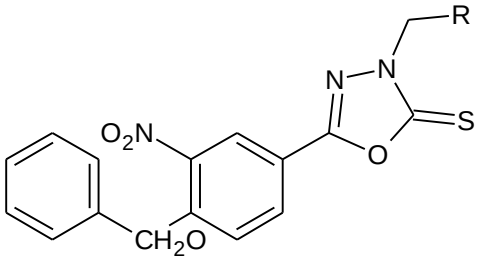
2

Joshi et al., [24] (1990) synthesized some quinazolinonyl oxadiazoles (3) and evaluated for their antibacterial and antifungal activity using cup-plate method.



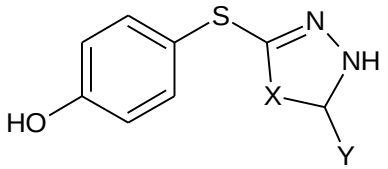
3

Varma et al., [25] (1991) reported the synthesis and antilieshmanial activity of 4-heterocyclic-aminomethyl-2-(3'-nitro-4-benzyloxyphenyl)-1,3,4-oxadiazolin-5-thiones (4).



4

James et al., [26] (1993) reported the cyclooxygenase and 5-lipoxygenase inhibitory acticity of 2,6-di-t-butyl phenols (5) linked by a sulfur atom to 1,3,4-thiadiazole and 1,3,4-oxadiazoles.

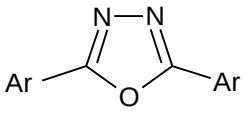


5

X = O , S

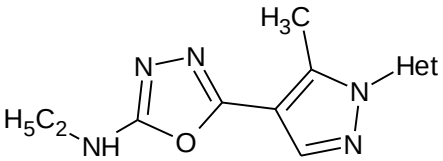
Y = O, S , NCN , NH

Fray et al., [27] (1995) reported the synthesis of 2,5-diaryl-1,3,4-oxadiazoles (6) as platelet aggregation inhibitors.



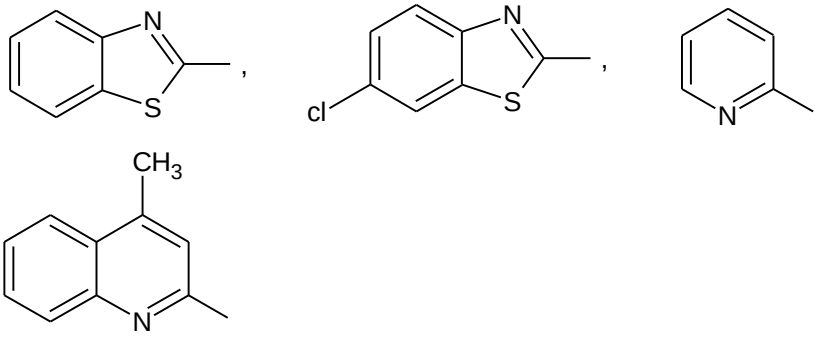
6

Kapoor et al., [28] (1997) reported the synthesis and *invitro* antibacterial, antifungal and antimycobacterial evaluation of some new oxadiazolyl pyrazoles (7).

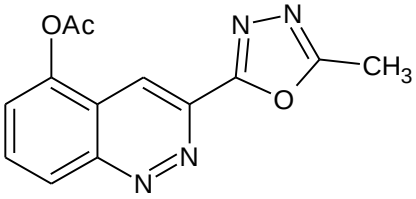


7

Het =

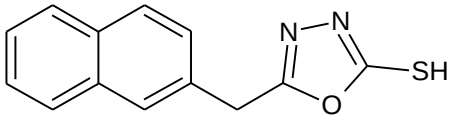


Menon et al., [29] (1997) synthesized a series of 2-methyl-5-(4-acetoxy quinolin-3-yl)-1,3,4-oxadiazoles (8) and evaluated for their antimicrobial activity using the bacteria *S.aureus (g+ve),E.coli(g-ve),fungi:A.niger and C.albicans* by the cup-plate method.



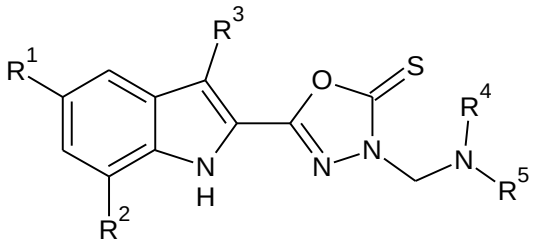
8

Mohammed et al., [30] (1998)S synthesized 5-naphthyl methyl-13,4-oxadiazoles (9) and evaluated for their anti-inflammatory activity.



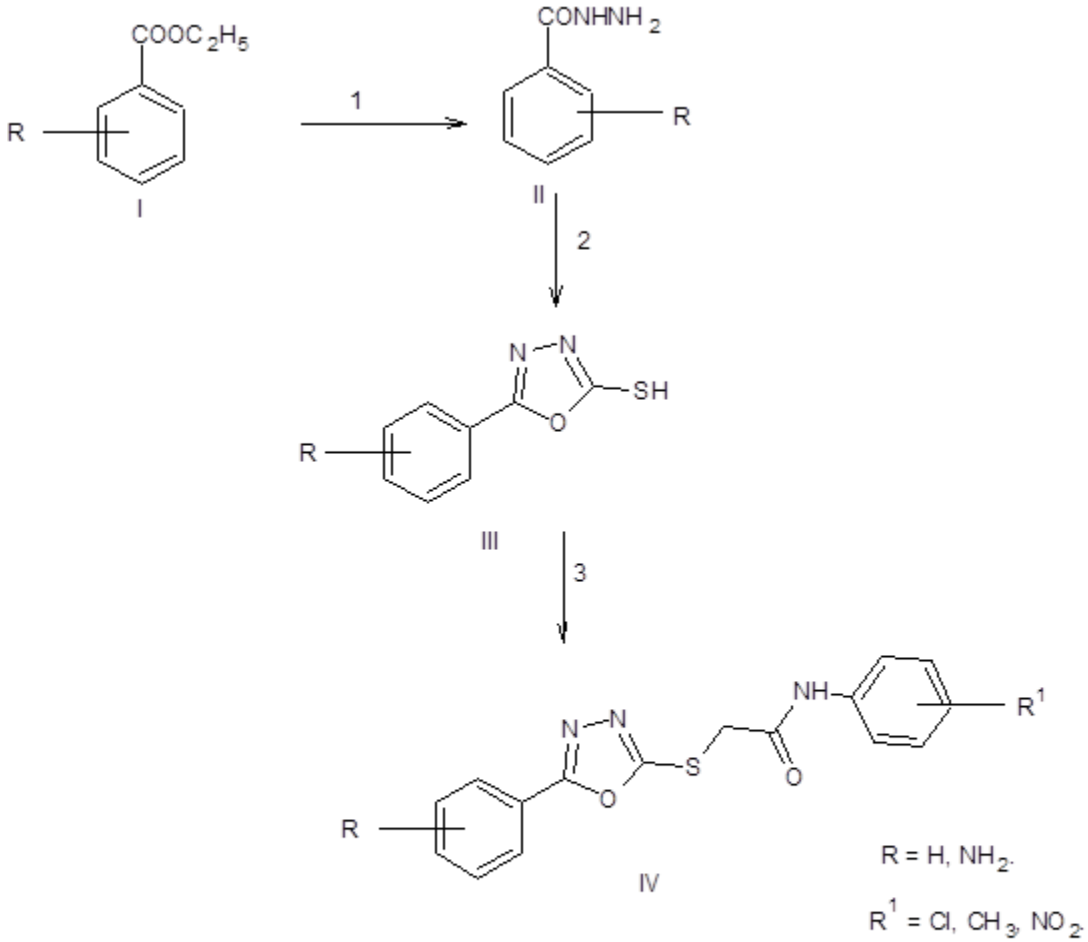
9

Sonar et al., [31] (1998) synthesized Mannich bases of 2-(5'-thio-1'3'4'-oxadiazol-2'-yl) indoles (10) and screened for their anti-inflammatory activity by paw edema method.



10

SCHEME



1. $NH_2NH_2.H_2O$ reflux for 4-5 hrs / MWI for 15 min
2. CS_2/Alc.KOH reflux for 16 hrs / MWI 22 Min.
3. Different 2-Chloro-N-phenylacetamide in dry pyridine fo 24 hrs/ MWI 27 Min

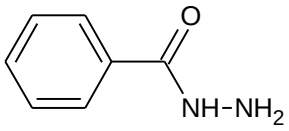
EXPERIMENTAL DETAILS

Synyhesis of benzoicacidhydrazide (ii)

A mixture of hydrazine hydrate (12ml, 0.24mol) andethylbezoate/ethyl-p-aminobenzoate (27.33gm,0.2mol) was taken into a round bottomed flask and heated under reflux for 15 min. Ethanol was added through the condensor to produce a clear solution, refluxed for another 4-5 hrs/ Mircrowave irradiation run time 15 min. The reaction was

monitored by TLC. After completion of the reaction, the excess of solvent was distilled off and the contents were cooled to room temperature. The crystals of acid hydrazide formed were filtered, dried and further purified by recrystallization from ethanol.

Structure

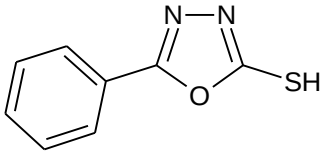


(II)

Form : white crystalline compound
Molecular formula : $C_7H_8N_2O$
Molecular weight : 136.15
Melting point : 112-114^{0}C (Lit: 113-115^{0}c)
TLC: Rf : 0.45 (n-hexane: ethylacetate-3:2)

Synthesis of 5-phenyl-1,3,4-oxadiazole-2-thiol (iii)

A mixture of benzoic acidhydrazide (II, 0.1mol) in ethanol (30ml), KOH (0.1mol) in absolute ethanol (50ml) and carbon disulfide (CS_2) was refluxed for about 16hrs//Mircrowave irradiation run time 22 min. Till evolution of hydrogen sulfide was ceased. The reaction mixture was cooled at room temperature and poured over crushed ice. On acidification with dil. HCl, the required oxadiazole was precipitated. The solid mass that separated out was filtered, dried and recrystallized from ethanol to get desired product as a solid. The yield of the compound was found to be 58%. The purity of the compound was checked by TLC.

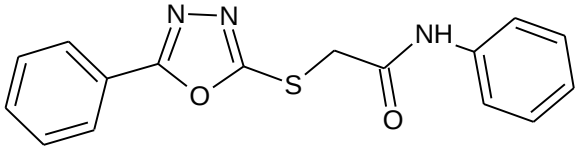


(III)

Form : light yellow crystalline compound
Molecular formula : $C_8H_6N_2OS$
Molecular weight : 178.21
Melting point : 237^{0}C
TLC: Rf : (n-hexane: ethylacetate-3:2)

Synthesis of n-phenyl-2-((5-phenyl-1,3,4-oxadiazole-2-yl)sulfanyl)acetamide(iv)

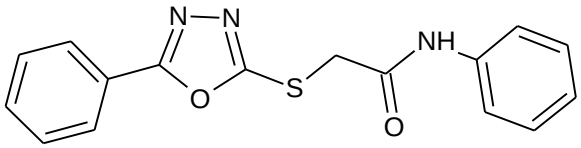
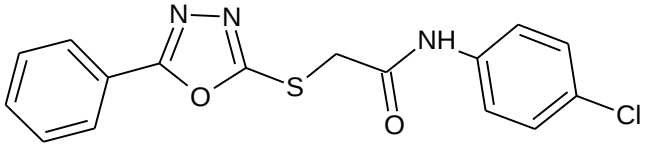
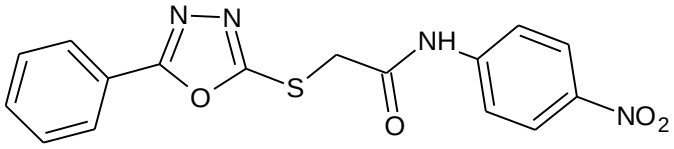
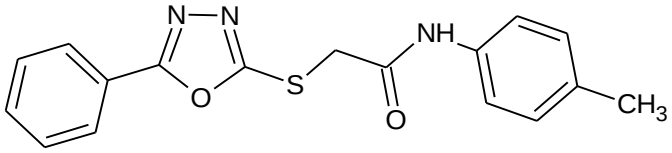
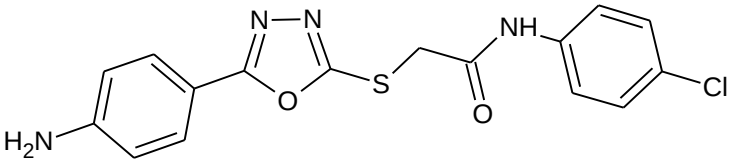
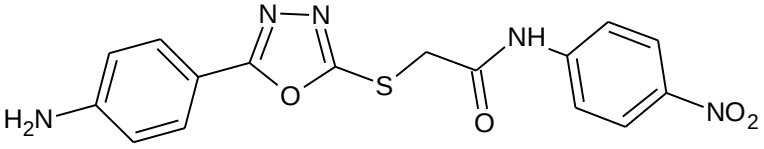
A mixture of 5-Phenyl-1,3,4-oxadiazole-2-thiol (III,0.01mol) and 2-chloro-N-phenyl acetamide (0.01mol) were refluxed in dry pyridine(20ml) for 24hrs/ Mircrowave irradiation run time 27 min. The rection mixture was then poured into a beaker containing ice cold water, the solid obtained was filtered , whashed with water and recrystalized from alcohol to yield white coloured crystals of N-Phenyl-2-((5-phenyl-1,3,4-oxadiazole-2-yl)sulfanyl)acetamide.



(IVa, R,R^1 = H)

Form	: light yellow crystalline	Molecular weight	: 311.35
compound		Melting point	: 242-244^{0}C
Molecular formula	: $C_{16}H_{13}N_3O_2S$	TLC: Rf	: (n-hexane: ethylacetate-3:2)

Table-I List of Synthesised Compounds

S.NO	STRUCTURE	IUPAC NAME
1		*N*-phenyl-2-[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide
2		*N*-(4-chlorophenyl)-2-[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide
3		*N*-(4-nitrophenyl)-2-[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide
4		*N*-(4-methylphenyl)-2-[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide
5		2-{[5-(4-aminophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}-*N*-(4-chlorophenyl)acetamide
6		2-{[5-(4-aminophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}-*N*-(4-nitrophenyl)acetamide

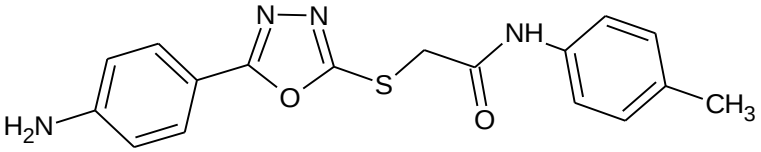
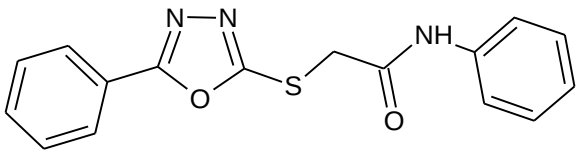
7		2-{[5-(4-aminophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}-*N*-(4-methylphenyl)acetamide

TABLE-II Physical data of N-Phenyl-2-((5-phenyl-1,3,4-oxadiazole-2-yl)sulfanyl)acetamide(IV)

S.No	Compound	Substituents		Molecular Formula	Mol. Weight	M.P (^{0}C)	Conventional Yield (%)	MWI Yield (%)
		R	R^1					
1.	IVa	H	H	$C_{16}H_{13}N_3O_2S$	311	243-245	45	89
2.	IVb	H	Cl	$C_{16}H_{12}ClN_3O_2S$	345	235-237	51	93
3.	IVc	H	NO_2	$C_{16}H_{12}N_4O_2S$	356	241-243	41	86
4.	IVd	H	CH_3	$C_{17}H_{15}N_4O_2S$	325	248-251	45	91
5.	IVe	NH_2	Cl	$C_{16}H_{13}Cl\ N_4O_2S$	360	233-235	49	94
6.	IVf	NH_2	NO_2	$C_{16}H_{13}N_5O_2S$	371	221-223	53	96
7.	IVg	NH_2	CH_3	$C_{17}H_{16}N_4O_2S$	340	229-231	50	95

Spectral data of N-Phenyl-2-((5-phenyl-1,3,4-oxadiazole-2-yl)sulfanyl)acetamide(iva-h)



N-phenyl-2-[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide

(IVa, R,R^1 = H)

Form : light yellow crystalline compound
Molecular formula : $C_{16}H_{13}N_3O_2S$
Molecular weight : 311.35
Melting point : 242 - 244^{0}C
TLC: Rf : (n-hexane: ethylacetate-3:2)
Solubility : methanol
IR (KBr) Cm^{-1} : 3328 (NH), 1674(C=O), 1616(C=N) & 1544(C=C).
NMR Spectra (δ ppm) : 10.4(S, 1H, -CONH), 7.2 – 7.6(M, 10H, Ar-H) & 4.4 (S, 2H, CH2)
Mass Spectra : Molecular ion peak (M+1) at m/z 312.

CONCLUSION

Oxadiazole derivatives found to possess certain specific pharmacological activities. By taking the view in the mind we are prepared some oxadiazole derivatives by conventional and microwave irradiation method. In this work we compared the conventional and microwave irradiation methods. The results were found very effective yields in less time when compared with conventional method; it is safe and eco-friendly method for the synthesis of various organic compounds in the way of new drug discovery. It is highly recommended for the

synthesis of many organic reactions which may not be hazardous than other methods.

Acknowledgements

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