



A REVIEW ON SYNTHETIC AND THERAPEUTIC ASPECTS OF 1, 3, 4-OXADIAZOLE DERIVATIVES AND FUTURE PERSPECTIVE

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ABSTRACT

Oxadiazoles are five-membered heteroaromatic rings containing two carbons, two nitrogens, and one oxygen atom, and they exist in different regioisomeric forms. Oxadiazoles are frequently occurring motifs in drug like molecules, and they are often used with the intention of being bioisosteric replacements for ester and amide functionalities. 1,3,4-oxadiazoles possessed a wide range of biological activities like antimicrobial, analgesic, anti-inflammatory, hypnotic and sedative, CNS stimulants, anticonvulsant, antihypertensive, anti-HIV, antitubercular, anticancer, antiemetic, antidiabetic activities while 1,3,4-oxadiazole with aromatic substitution at 2nd and 5th position had been reported to be associated with antimicrobial, anti-inflammatory, anticancer, analgesic and anticonvulsant activity.

KEYWORDS: Regioisomeric, bioisosteric, antihypertensive, anti-HIV, antitubercular, anticancer etc.

INTRODUCTION

Heterocyclic chemistry is branch of organic chemistry in which study of cyclic compounds containing the ring atoms are of carbon and some other elements like N, S and O.^[1] In chemistry, methine is a trivalent functional group =CH-, derived formally from methane. It consists of a carbon atom bound by two single bonds and one double bond, where one of the single bonds is to a hydrogen. The group is also called methyne or methene; its IUPAC systematic name is methylylidene or methanylylidene. Oxadiazole is derived from furan by

replacement of two methine (-CH=) group by two pyridine type nitrogen (-N=).^[2] There are four possible isomers of oxadiazole forms (**1, 2, 3, and 4**) depending on the position of nitrogen atom in the ring and are numbered as shown below. Oxadiazole is a heterocyclic aromatic chemical compound with the molecular formula C₂H₂N₂O. There are four isomers of oxadiazole: **Oxadiazole** is a heterocyclic aromatic chemical compound with the molecular formula C₂H₂N₂O. There are four isomers of oxadiazole:

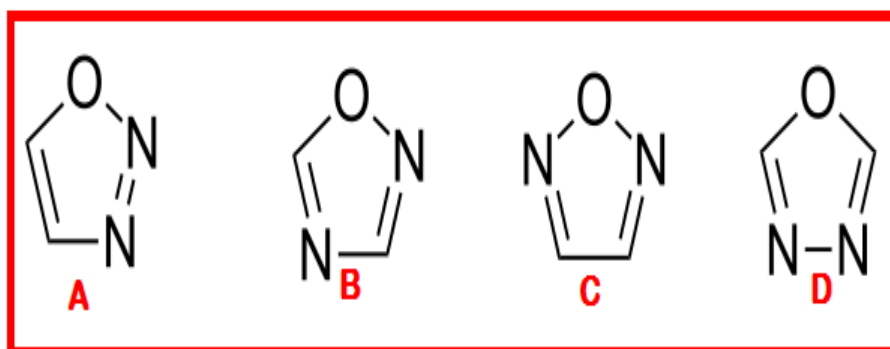


Fig 1: Four possible isomers of oxadiazole

A.1,2,3-oxadiazole. B.1,2,4-oxadiazole. C.1,2,5-oxadiazole (furazan). D. 1, 3, 4-oxadiazole

1,2,4-Oxadiazole, 1,2,5-oxadiazole, and 1,3,4-oxadiazole are known, but the 1,2,3-isomer is unstable and reverts to the diazoketone tautomer.^[3] The stable oxadiazoles

appear in a variety of pharmaceutical drugs including raltegravir, butalamine, faspion, oxolamine, and pleconaril.

Chemistry of oxadiazole

Oxadiazole, a very weak base due to inductive effect of the extra heteroatom. The replace of two $-CH=$ groups in furan by two pyridine type ($-N=$) lowers aromaticity of resulting oxadiazole ring to an extent that the oxadiazole ring exhibit character of conjugated diene. The electrophilic substitutions in oxadiazole ring are extremely difficult at the carbon atom because, the relatively low electron density on the carbon atom which can be attributed to electron withdrawal effect of the pyridine type nitrogen atom. If oxadiazole ring is substituted with electron-releasing groups, the attack of electrophiles occurs at nitrogen. The ring is generally resistant to nucleophilic attack.

1, 3, 4-oxadiazole

1,3,4-oxadiazole is a five membered heterocyclic aromatic compound containing two nitrogen atom at position three and four and one oxygen atom present at position one. 1,3,4 oxadiazole is thermally stable than other oxadiazoles, these oxadiazole are very important compound in medicinal chemistry due to their biological activities, during last few years.^[4]

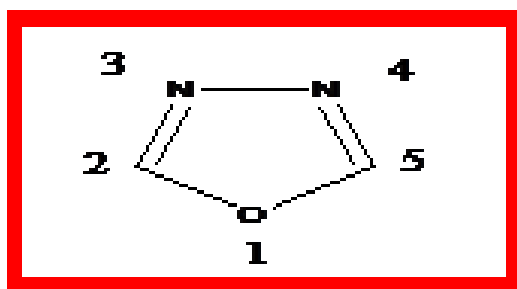


Fig 2: 1, 3, 4-oxadiazole

Furazan

Furazan, or 1,2,5-oxadiazole, is an heterocyclic aromatic organic compound consisting of a five-atom ring containing 1 oxygen and 2 nitrogen atoms. The furazan ring system is also found in the steroid furazabol.



Fig 3: Furazan

SYNTHESIS OF OXADIAZOLES

M.C Hosur reported synthesis of 2-mercapto-5-aryl-1, 3, 4-oxadiazole from the substituted acid hydrazide in presence of CS_2/KOH . This method is very popular gives high yields are consistently observed. A limiting factor is

Furazan and its derivatives are obtained from the oxime derivatives of 1, 2-diketones.

Synthesis

In theory the simplest means of producing furazan is the cyclic-dehydration of glyoxime (the di-oxime of glyoxal), however the instability of furazan to high temperature or extremes of pH requires that this process be performed carefully. The formation of furazan from glyoxime is also exothermic and takes place with the copious evolution of noxious gases. The reaction may be achieved by heating glyoxime to $150^\circ C$ in the presence of succinic anhydride; furazan will evaporate at this temperature and thus is continuously removed from the reaction mixture.^[5]

Derivatives

3, 4-Dimethylfurazan (b. p. $154-159^\circ C$) is prepared by an analogous process by dehydrating dimethylglyoxime [6]. A variety of related derivatives are known, including diphenyl- and methylethylfurazan.

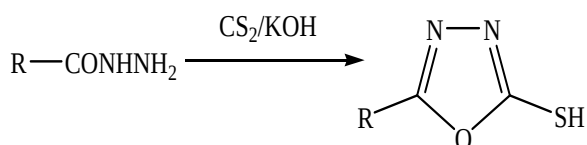
Carboxylic acid derivatives

Potassium permanganate oxidizes 3,4-dimethylfurazan first to methylfurazancarboxylic acid and then to furazandicarboxylic acid. By warming oxyfurazan acetic acid with excess of potassium permanganate, oxyfurazancarboxylic acid is obtained. It crystallizes as prisms (m.p. $175^\circ C$). Furazancarboxylic acid (m.p. $107^\circ C$) is prepared by oxidation of furazanpropionic acid with potassium permanganate. It dissolves in base to give nitrosocyanacetate.

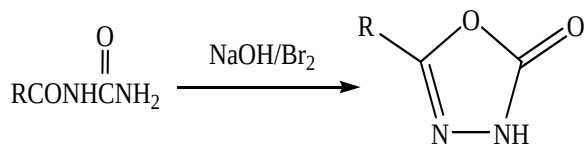
Diaminofurazan

The energetic precursor, diaminofurazan, can be prepared by heating diaminoglyoxime with potassium hydroxide followed by cooling to give white crystals. Like many other furazans, diaminofurazan forms stable complexes with copper (II) salts.

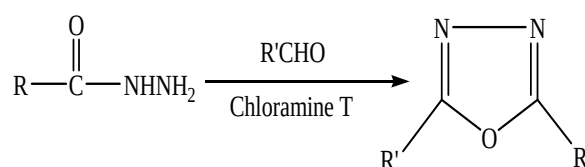
a long reaction time. Number of examples are shown in literature employing this methodology for synthesis of 1, 3, 4-oxadiazole thione / thiol derivatives.^[7]



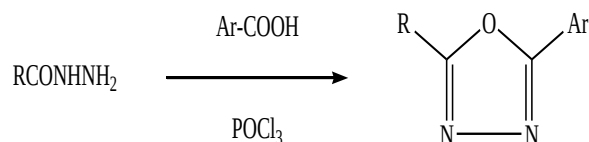
H. Singh and his groups reported synthesis of 2-aryl methyl-1, 3, 4-oxadiazole-5-ones produce acylurea using bromine in NaOH.^[8]



S. P. Singh and groups reported the synthesis 1, 3, 4-oxadiazole through a one pot procedure involving the reaction of acylhydrazide with aldehydes followed by in-situ cyclization using Chloramine T as an oxidizing agent.^[9]

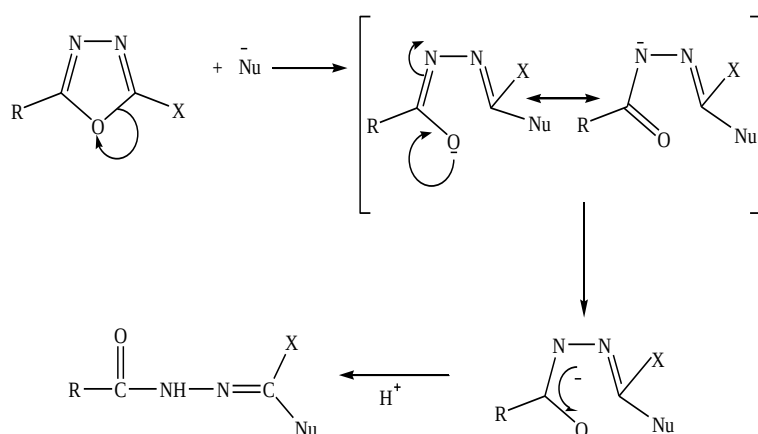
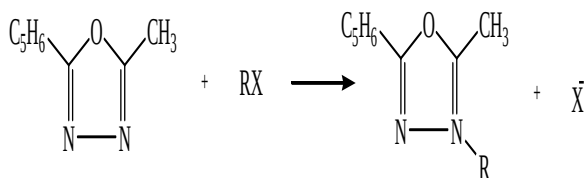


Formation of disubstituted -1, 3, 4-oxadiazole through cyclodehydrogenation by using phosphorus oxychloride (POCl_3) has also been used in various literatures. Condensation of various alkyl hydrazides with substituted aromatic acids in presence of POCl_3 which gives respective 2-alkyl-5-aryl-1, 3, 4-oxadiazoles.



Reaction of electrophiles

The 1, 3, 4-oxadiazole undergoes different organic reactions. Due to low π -electron density on the carbon atom, the attack of electrophile commonly occurs at the position 3 with the formation of 1, 3, 4-oxadiazolium salts. The alkylation of 2-alkoxy-1, 3, 4-oxadiazole with alkyl halides produces oxadiazolium salt which undergo O-dealkylation to provide 4-alkyl-oxadiazolin-5-ones. 2, 5-Diphenyl-1, 3, 4-oxadiazole can be nitrated or sulfonated by conc. HNO_3 and oleum. This result in to attack on phenyl ring itself.



Thermal reactions

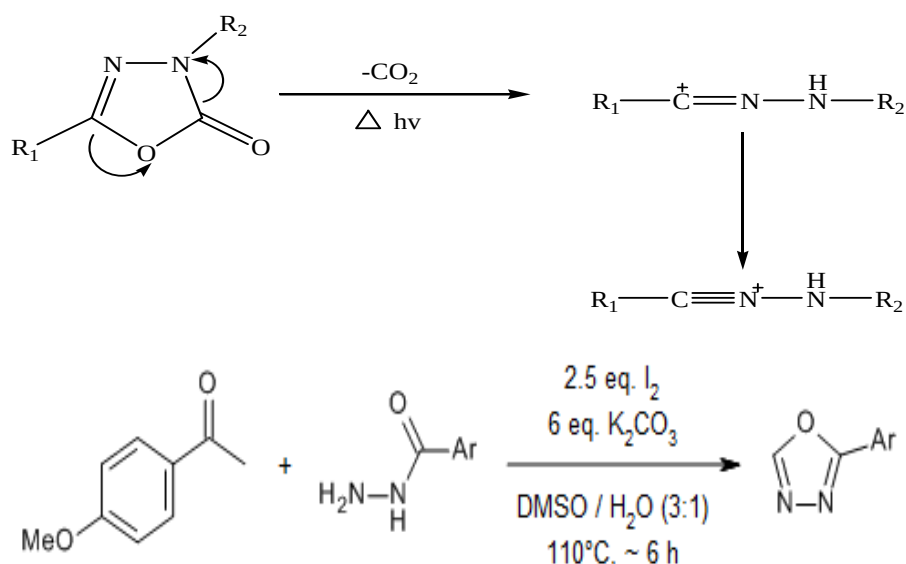
1, 3, 4-Oxadiazole is thermally stable and stability of ring is increased with the substitution of the aryl groups.

Attack of electrophiles (R) at 3rd position

Reaction of nucleophiles

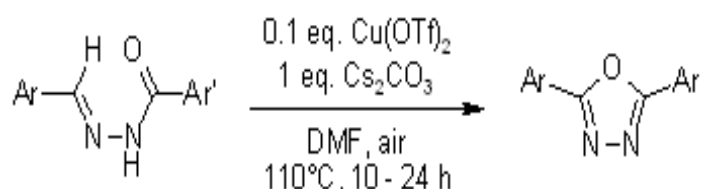
Reactions of Oxadiazoles with nucleophiles are also reported. The carbon atoms in 1, 3, 4-oxadiazole ring are relatively with low π electron density and therefore attack of nucleophiles occurs at on that carbon atom. The reaction proceeds with nucleophilic substitution or with ring cleavage. 1, 3, 4-oxadiazole substituted containing halogen or sulfonyl group at the position-2 easily undergo nucleophilic substitution reaction. The reaction of Oxadiazoles such as 2-chloro-1, 3, 4-oxadiazole with nucleophiles such as amines, thiourea or azide proceeds with the substitution of chloro group by nucleophile and result in the corresponding 2-substituted-1, 3, 4-Oxadiazoles.

However 1, 3, 4-oxadiazolin-5 ones undergo thermal and photochemical ring opening reaction with the loss of carbon dioxide to provide nitrilimine.



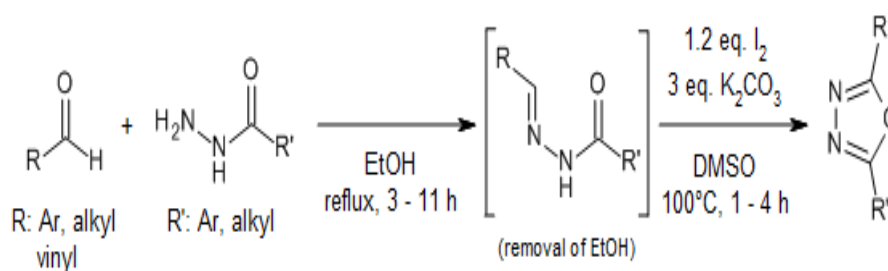
In a direct annulation of hydrazides with methyl ketones for the synthesis of 1,3,4-oxadiazoles, the use of K_2CO_3 as a base achieves an unexpected and highly efficient C-

C bond cleavage. This reaction is proposed to go through oxidative cleavage of Csp³-H bonds, followed by cyclization and deacylation.^[10]



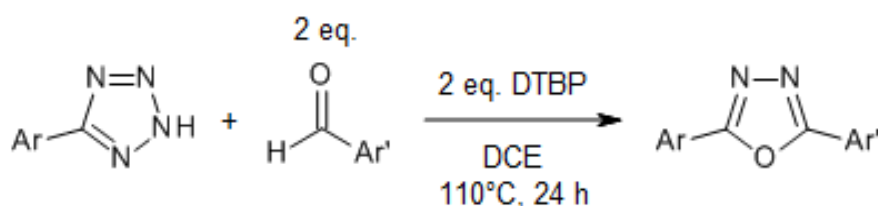
A direct access to symmetrical and unsymmetrical 2,5-disubstituted [1,3,4]-oxadiazoles has been accomplished through an imine C-H functionalization of N-arylidenearylhydrazide using a catalytic quantity of

$Cu(OTf)_2$. These reactions can be performed in air atmosphere and moisture making it exceptionally practical for application in organic synthesis.^[11]



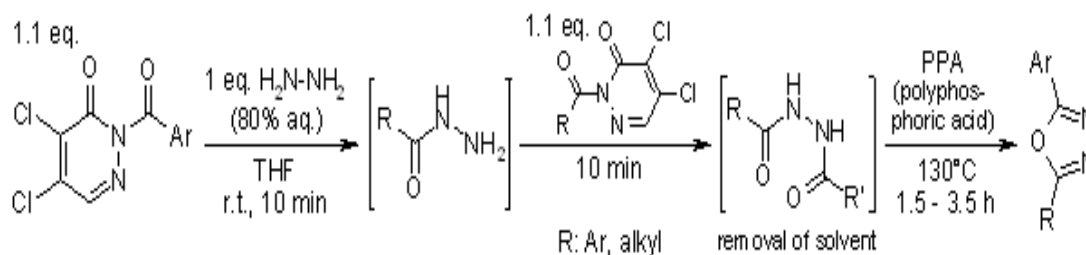
Stoichiometric molecular iodine mediates a practical and transition-metal-free oxidative cyclization of acylhydrazones into 1,3,4-oxadiazoles in the presence of potassium carbonate. Even crude acylhydrazone substrates obtained from the condensation of aldehydes

and hydrazides can be converted. A series of symmetrical and asymmetrical 2,5-disubstituted 1,3,4-oxadiazoles can be conveniently generated in an efficient and scalable fashion.^[12]



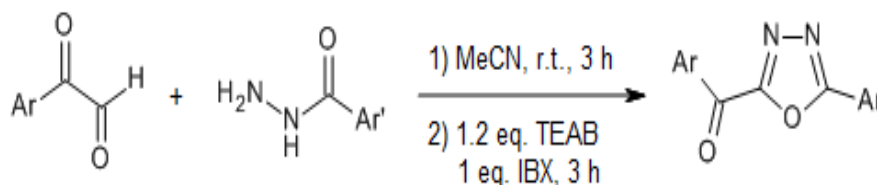
A radical-promoted cross-dehydrogenative coupling strategy enables a metal- and base-free one-pot synthesis of 2,5-diaryl 1,3,4-oxadiazoles via *N*-acylation of aryl tetrazoles with aryl aldehydes, followed by thermal

rearrangement. A broad range of aryl tetrazoles and aryl aldehydes deliver the corresponding products in good yields.^[13]



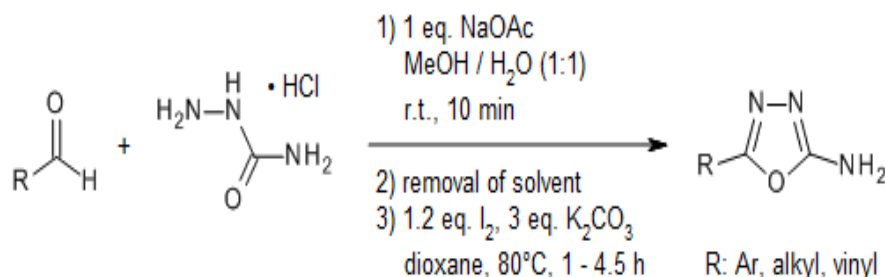
Symmetric and unsymmetric 1,3,4-oxadiazoles were synthesized in situ from hydrazine hydrate and the corresponding 2-acyl-4,5-dichloropyridazin-3-ones as

acylating agents in polyphosphoric acid (PPA) or $\text{BF}_3 \cdot \text{OEt}_2$ in excellent yields.^[14]



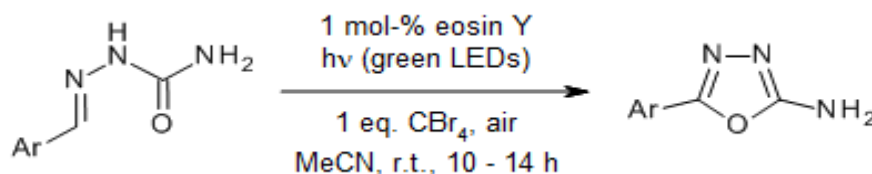
A 2-iodoxybenzoic acid/tetraethylammonium bromide mediated oxidative cyclization of hydrazide-hydrazones generated in situ from aryl glyoxal and hydrazides

enables an efficient and high-yielding protocol for the preparation of α -keto-1,3,4-oxadiazoles under mild conditions in short reaction times.^[15]



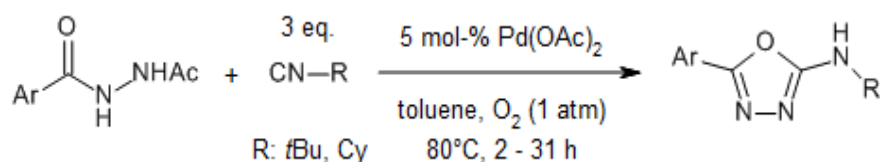
A transition-metal-free condensation of semicarbazide/thiosemicarbazide with aldehydes followed by I_2 -mediated oxidative C-O/C-S bond

formation provides 2-amino-substituted 1,3,4-oxadiazoles and 1,3,4-thiadiazoles in an efficient and scalable fashion.^[16]



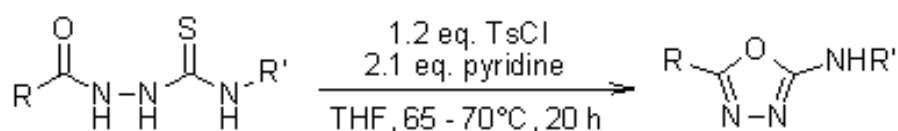
A highly efficient eosin Y catalyzed oxidative heterocyclization of semicarbazones was established under visible-light photoredox catalysis using CBr_4 as a bromine source. The protocol renders a rapid, mild, and

efficient access to valuable 5-substituted 2-amino-1,3,4-oxadiazoles in an operationally simple way utilizing visible light and atmospheric oxygen.^[17]

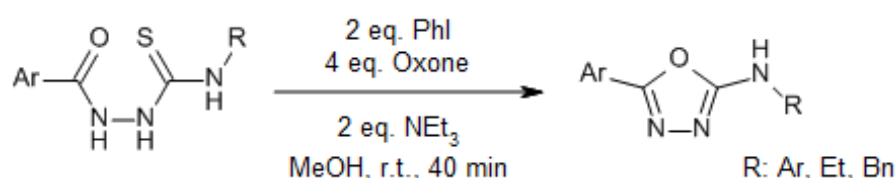


Efficient palladium-catalyzed sequential isocyanide insertions into N-H and O-H bonds of hydrazides followed by oxidative annulation provide a convenient

access to valuable 2-amino-1,3,4-oxadiazoles and their derivatives [18]



A facile and general protocol for the preparation of 2-amino-1,3,4-oxadiazoles relies on a tosyl chloride/pyridine-mediated cyclization of thiosemicarbazides that consistently outperforms the analogous semicarbazide cyclizations. Various 5-alkyl- and 5-aryl-2-amino-1,3,4-oxadiazoles have been prepared in good yields.^[19]



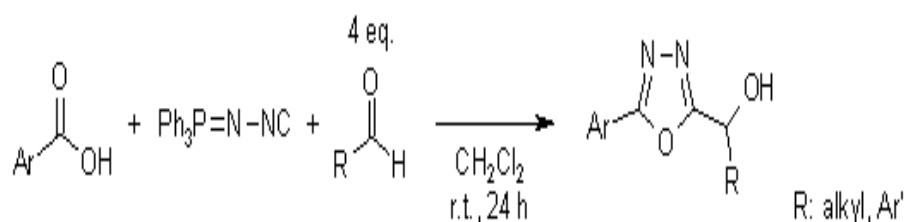
An oxidative desulfurization approach enables the construction of oxadiazole and thiadiazole heterocycles in the presence of iodobenzene and Oxone. The use of

iodobenzene and the inexpensive readily available oxidant Oxone makes the reaction system simple and versatile for desulfurization.^[20]



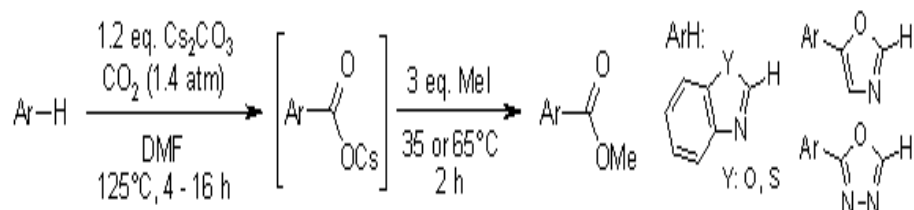
The reaction of a thiosemicarbazide intermediate with EDC·HCl in DMSO or *p*-TsCl, triethylamine in *N*-methyl-2-pyrrolidone gives the corresponding 2-amino-

1,3,4-oxadiazoles and 2-amino-1,3,4-thiadiazoles through regioselective cyclization processes.^[21]



N-Isocyaniminotriphenylphosphorane, aldehydes, and benzoic acids undergo a one-pot, three-component

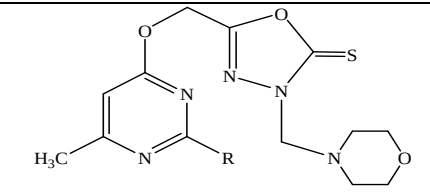
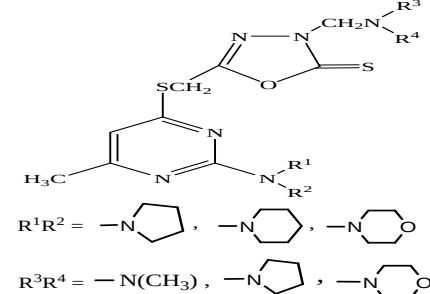
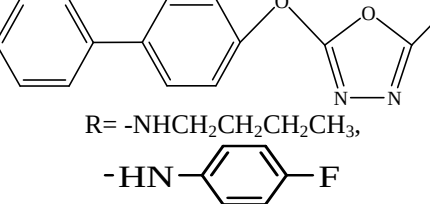
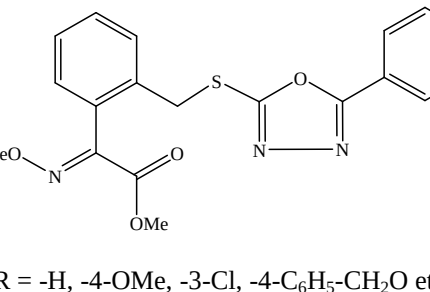
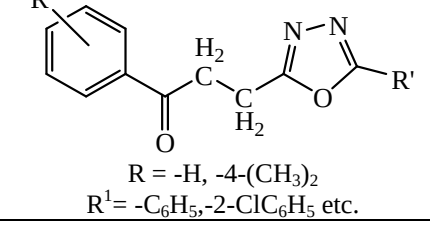
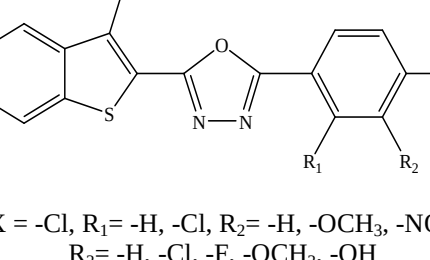
reaction under mild conditions to afford 2-aryl-5-hydroxyalkyl-1,3,4-oxadiazoles in good yields.^[22]

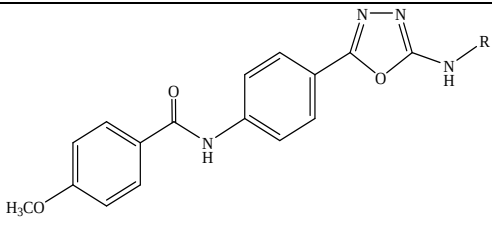
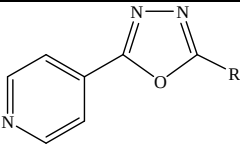
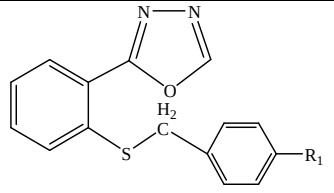
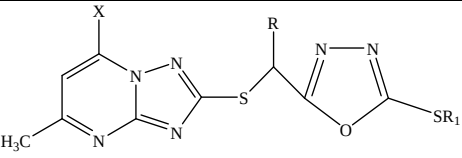
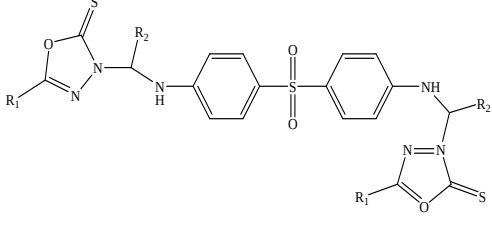
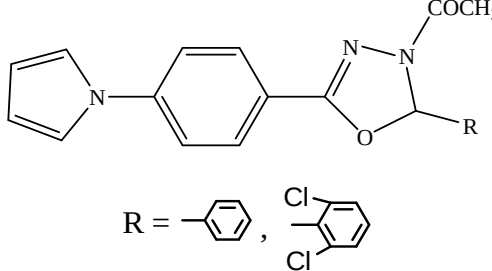
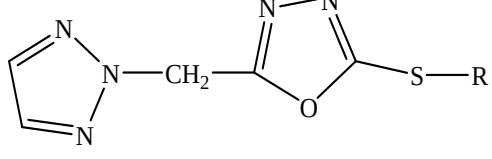


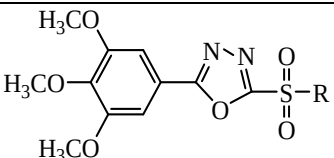
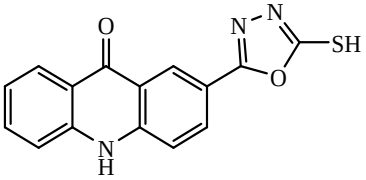
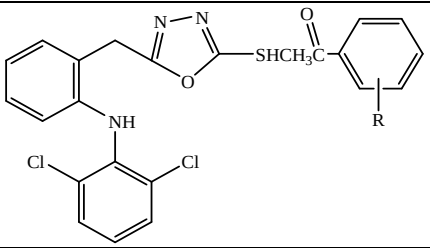
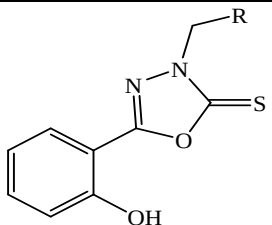
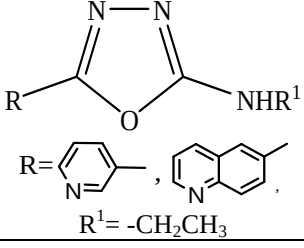
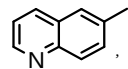
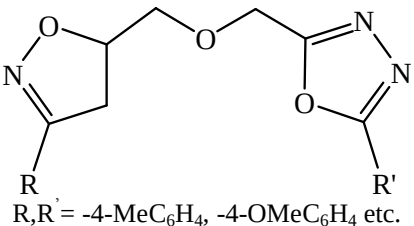
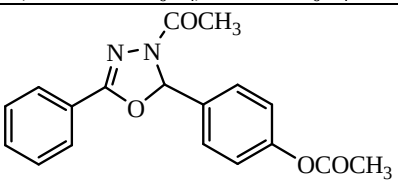
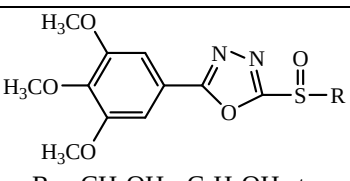
A simple and straightforward method for the direct carboxylation of aromatic heterocycles such as oxazoles, thiazoles, and oxadiazoles using CO_2 as the C1 source

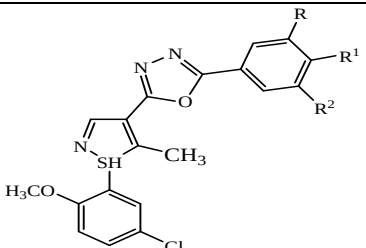
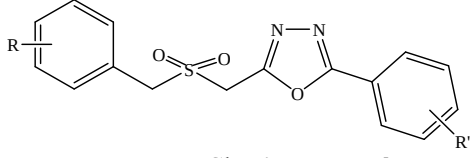
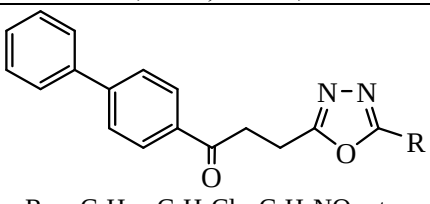
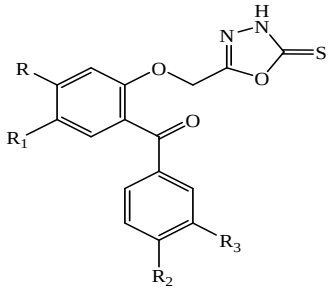
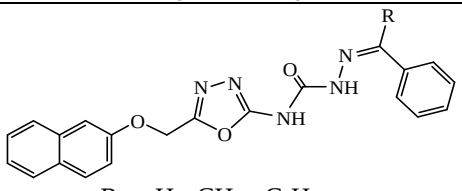
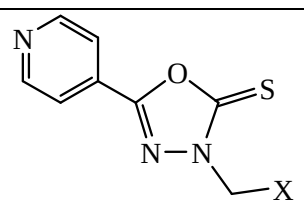
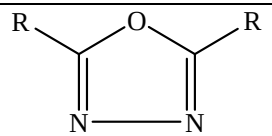
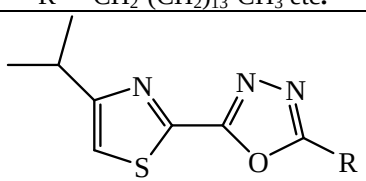
requires no metal catalyst and only Cs_2CO_3 as the base. A good functional group tolerance is achieved.^[23]

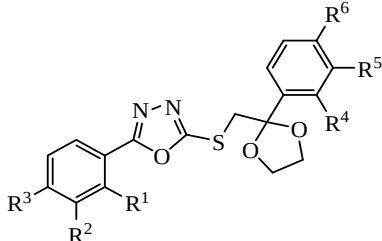
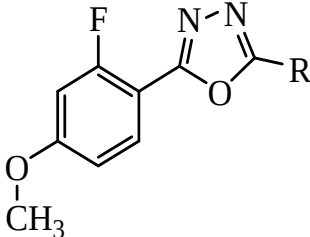
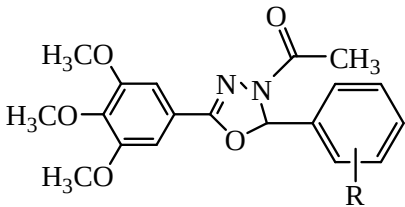
STRUCTURE OF DIFFERENT DERIVATIVES OF 1, 3, 4-OXADIAZOLE AND THEIR PHARMACOLOGICAL ACTIVITY

Sl. No.	Structure	Reported Activities	References
1.	 R = $-\text{SCH}_3$, $-\text{NHCH}_2\text{C}_6\text{H}_5$, $-\text{N}(\text{CH}_3)_2$ etc.	Anti-inflammatory.	Virginija Jakubkiene et al. ²⁴
2.	 $\text{R}^1\text{R}^2 = -\text{N}(\text{CH}_3)_2$, $-\text{N}(\text{CH}_3)_2$, $-\text{N}(\text{CH}_3)_2$ $\text{R}^3\text{R}^4 = -\text{N}(\text{CH}_3)_2$, $-\text{N}(\text{CH}_3)_2$, $-\text{N}(\text{CH}_3)_2$	Anti-inflammatory.	Milda M.B. et al. ²⁵
3.	 R = $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{HN}-\text{C}_6\text{H}_4-\text{F}$	Anti-inflammatory.	Mohammad Amir. et al. ²⁶
4.	 R = $-\text{H}$, $-\text{4-OMe}$, $-\text{3-Cl}$, $-\text{4-C}_6\text{H}_5\text{-CH}_2\text{O}$ etc.	Antifungal.	Yan Li. et al. ²⁷
5.	 R = $-\text{H}$, $-\text{4-(CH}_3)_2$ $\text{R}' = -\text{C}_6\text{H}_5$, $-\text{2-ClC}_6\text{H}_5$ etc.	Anti-inflammatory and Analgesic	Mymoona Akhter. et al. ²⁸
6.	 X = $-\text{Cl}$, $\text{R}_1 = -\text{H}$, $-\text{Cl}$, $\text{R}_2 = -\text{H}$, $-\text{OCH}_3$, $-\text{NO}_2$, $\text{R}_3 = -\text{H}$, $-\text{Cl}$, $-\text{F}$, $-\text{OCH}_3$, $-\text{OH}$	Antimicrobial	Rakesh C. et al. ²⁹

7.	 R = -C₆H₄F, -C₆H₄Cl, -C₆H₄-Br etc	Antimicrobial, Antimycobacterial	S.Guniz Kucukguzel.et al. ³⁰
8.	 R = -CH₃, -CF₃, -CH₂Cl, -C₁₅H₃₁ etc.	Antimycobacterial	Gabriel Navarrete-Vazquez.et al. ³¹
9.	 R₁ = -H, -F, -Cl. R₂ = -NH₂, -SH, -SCH₃, -SC₂H₅ etc.	Anticonvulsant	Afshin Z.et al. ³²
10.	 X = -H, -CH₃ ; R = -H, -CH₃, R₁ = -4-ClC₆H₄CH₂, -2-FC₆H₄CH₂ etc.	Antifungal	Guang-Fu Y.et al. ³³
11.	 R₁ = -C₆H₅, -4-NO₂-C₆H₅ ; R₂ = furfuryl-, Phenyl- etc.	Antimycobacterial	Mohammad Shaharyar.et al. ³⁴
12.	 R = , 	Antibacterial and Antitubercular	H.M.Vagdevi.et al ³⁵
13.	 R = -C₆H₅COCH₂, -4-ClC₆H₄COCH₂ etc	Antifungal	XU Liang-Z.et al. ³⁶

14.	 R = -CH₃, -H₂C-CH=CH₂ etc.	Antifungal	Song Yang.et al. ³⁷
15.		Antimicrobial	Jumat S.et al. ³⁸
16.		Antiinflammatory, Analgesic and Ulcerogenicity	Kailash G. Bothara.et al. ³⁹
17.	 R = -NH₂C₆H₅, -NH-C₆H₄(3-CH₃) etc	Anticancer Agent	Nadia M.Mahfouz.et al. ⁴⁰
18.	 R = , , R¹ = -CH₂CH₃	Anti-inflammatory	FA Omar.et al. ⁴¹
19.	 R, R' = -4-MeC₆H₄, -4-OMeC₆H₄ etc.	Anti-inflammatory and Analgesic	B.Jayashankar.et al. ⁴²
20.		Vaso relaxant	Gopalan Kutty Nampurath.et al. ⁴³
21.	 R = -CH₃OH, -C₂H₅OH etc	Antifungal	Pinaki S.B.et al. ⁴⁴

22.	 R, R¹, R² = -H, -Br, -CH₃, -Cl etc.	Antibacterial	Sheena Shashikanth.et al. ⁴⁵
23.	 R = -H, -4-Cl; R' = -H, -2-Cl	Antimicrobial and cytotoxic	V.Padmavathi.et al. ⁴⁶
24.	 R = -C₆H₅, -C₆H₄Cl, -C₆H₄NO₂ etc.	Anti-inflammatory and Analgesic agent	Asif Husain.et al. ⁴⁷
25.	 R = -H, -Br, R₁ = -H, -Cl, -CH₃, R₂ = -H, R₃ = -H, -CH₃	Antimicrobial	Sheena Shashikanth.et al. ⁴⁸
26.	 R = -H, -CH₃, -C₆H₅ etc.	Anticonvulsant	Harish R.et al. ⁴⁹
27.		Antimycobacterial	Maria Grazia Mamolo.et al. ⁵⁰
28.	 R = -CH₂-(CH₂)₁₃-CH₃ etc.	Antibacterial and Antifungal	Abdul Rauf.et al. ⁵¹
29.	 R = -CH₃, -C₆H₅, -C₆H₄Cl etc.	Antimicrobial and Antitubercular	G.V.Suresh Kumar.et al. ⁵²

30.	 $R^1 = -OH, -H, R^2 = -H, -OMe, R^3 = -H, -OEt, -OMe, R^4 = -H, -2-Naphthyl, R^5 = -OMe, R^6 = -H, -F, -Br, -Cl, -OMe$ etc.	Antimycobacterial	Fliur M.et al. ⁵³
31.		Antimicrobial	Arun M. I.et al. ⁵⁴
32.	 $R = -2-F, -3-F, -4-F, -2-CF_3$ etc.	Anticancer	Baoan Song.et al. ⁵⁵

CONCLUSION

This review gives a future perspective of pronounced clinical, pharmacokinetic and pharmacodynamic profile of the various 1, 3, 4- oxadiazole derivatives and opening a new era for designing and synthesis of new oxadiazole scaffolds for the treatment various infectious and non communicable diseases. Thus the overview of this article gives a new idea for the development of novel 1, 3, 4-oxadiazoles as preclinical drug candidates which may be designed and produced via range of activities from the conventional medicinal chemistry approach to combinatorial biosynthesis.

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