



Oxadiazole: A biologically important heterocycle

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Abstract

Oxadiazole, a heterocyclic nucleus has attracted a wide attention of the chemist in search for the new therapeutic molecules. Out of its four possible isomers, 1, 3, 4-oxadiazole is widely exploited for various applications. A numbers of therapeutic agents such as HIV-integrase inhibitor **raltagravir**, a nitrofurantolone antibacterial **furamizole**, a potent PDF inhibitor **BB-83698**, antihypertensive agents **tiodazosin** and **nesapidil** are based on 1,3,4-oxadiazole moiety. The 1, 3, 4-oxadiazole undergoes number of reactions including electrophilic substitution, nucleophilic substitution, thermal and photochemical. The present review attempts to summarize the various routes of synthesis and the reactions of 1, 3, 4-oxadiazole and its derivatives and focus on their biological potential.

Key words: 1, 3, 4-Oxadiazole, Chemistry, Reactions, Syntheses, Biological activities.

Introduction

Oxadiazole is considered to be derived from furan by replacement of two methane (-CH=) group by two pyridine type nitrogen (-N=). There are four possible isomers of oxadiazole (**1**, **2**, **3**, **4**) depending on the position of nitrogen atom in the ring and are numbered as shown in Fig. 1 [1].

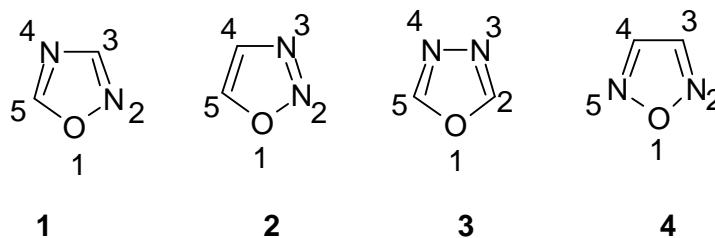


Fig.1: Isomers of oxadiazole

Literature survey reveals that particularly 1, 3, 4-oxadiazole derivatives exhibit wide range of biological activities including anticancer [2], anti-inflammatory [3], fungicidal [4], herbicidal [5], pesticidal, analgesic [6], anticonvulsant [7, 8], anti-HIV [9], antibacterial and plant growth regulator activities [10].

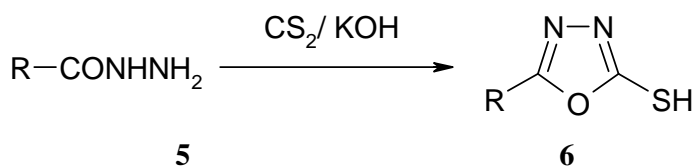
1, 3, 4-Oxadiazoles

2.1 Chemistry of oxadiazole

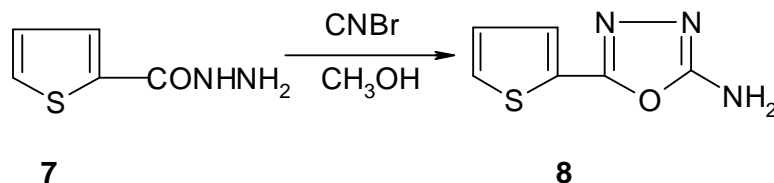
Oxadiazole is a very weak base due to the inductive effect of the extra heteroatom [11]. The replacement of two -CH= groups in furan by two pyridine type nitrogen (-N=) reduces aromaticity of resulting oxadiazole ring to such an extent that the oxadiazole ring exhibit character of conjugated diene. The electrophilic substitutions in oxadiazole ring are extremely difficult at the carbon atom because of the relatively low electron density on the carbon atom which can be attributed to electron withdrawal effect of the pyridine type nitrogen atom. However the attack of electrophiles occurs at nitrogen, if oxadiazole ring is substituted with electron-releasing groups. Oxadiazole ring is generally resistant to nucleophilic attack. Halogen-substituted oxadiazole, however, undergo nucleophilic substitution with replacement of halogen atom by nucleophiles. Oxadiazole undergo nucleophilic substitution similarly as occurring at an aliphatic sp^2 carbon atom [12]. The present manuscript specially emphasizes on chemistry, methods of synthesis and reactivity of 1, 3, 4-oxadiazole and its derivatives.

2.2 Syntheses of 1, 3, 4-oxadiazole backbone

M.C Hosur [13] reported synthesis of 2-mercapto-5-aryl-1, 3, 4-oxadiazole (**6**) from the properly substituted acid hydrazide (**5**) in presence of CS_2/KOH . (**Scheme 1**). This method is very popular since ease in workup and high yields are consistently observed. However, long reaction time is a limiting factor. Number of examples are cited in literature employing this methodology for synthesis of 1, 3, 4-oxadiazole thione / thiol derivatives [14-17]. M.A. Elborai et al [18] reported synthesis of 2-amino-5-(2'-thienyl)-1, 3, 4-oxadiazole (**8**) by the condensation of 2-thienyl hydrazide (**7**) with $CNBr$ (**Scheme 2**). It is a convenient method of synthesis of amino-1, 3, 4-oxadiazole because of shorter reaction time. More reports are cited in literature, which employed this method to obtain the 1, 3, 4- amines. [19-20].

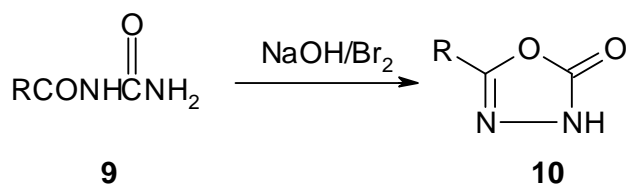


Scheme 1: Synthesis of 2-mercapto-5-aryl-1, 3, 4-oxadiazole using carbon disulphide in alkaline media

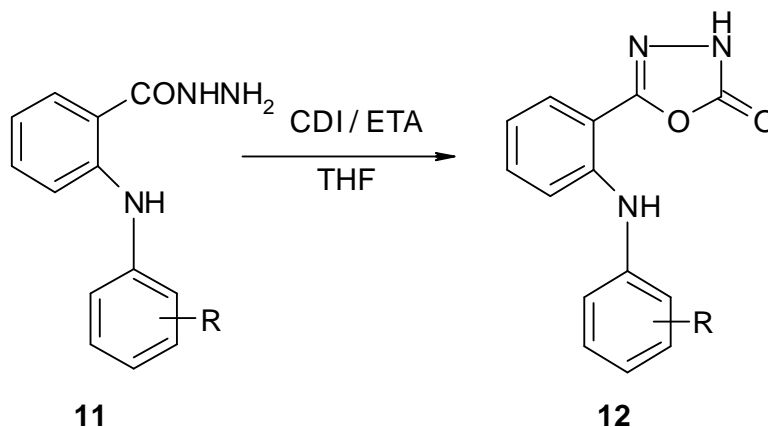


Scheme 2: Synthesis of 1, 3, 4-oxadiazole amine using cyanogen bromide

H. Singh and coworkers [21] reported synthesis of 2-arylmethyl- Δ^2 - 1, 3, 4-oxadiazoline-5-ones (**10**) from acylurea [**9**] using bromine in $NaOH$ (**Scheme 3**). D. H. Boschelli et al [22] synthesized substituted aryl type of (**12**) 1, 3, 4-oxadiazolone by reacting 1, 1'-carbonyldiimidazole (CDI) and triethylamine (TEA) in presence of tetrahydrofuran (THF) as solvent (**Scheme 4**).

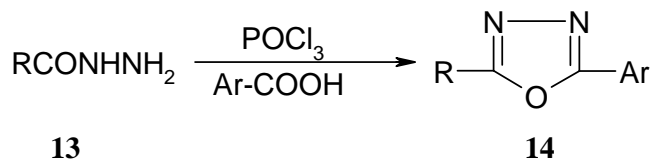


Scheme 3: Synthesis of 1, 3, 4-oxadiazolone using bromine in alkaline media

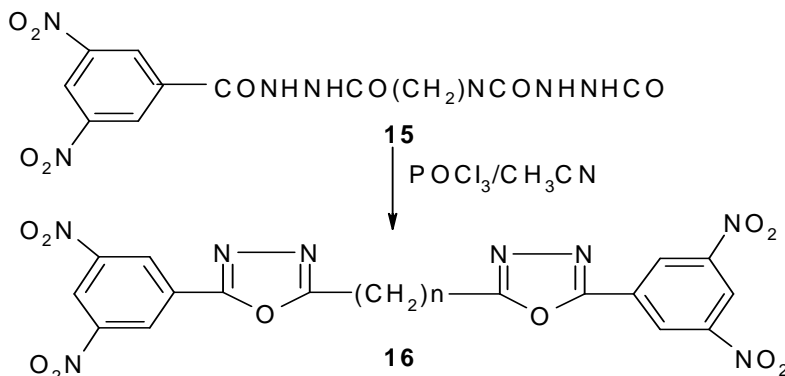


Scheme 4: Synthesis of 1, 3, 4-oxadiazolone using carbonyldiimidazole (CDI)

Formation of disubstituted-1, 3, 4-oxadiazole via cyclodehydrogenation using phosphorus oxychloride (POCl_3) has also been accounted in various literatures [23-26]. Condensation of various alkyl hydrazides (**13**) with substituted aromatic acids in presence of POCl_3 yielded respective 2-alkyl-5-aryl -1, 3, 4-oxadiazoles (**14**). (Scheme 5). N. Sikder et al [27] synthesized long chain bis-1, 3, 4-oxadiazoles (**16**), from the cyclization of N, N'-dinitrobenzoyl malonic or adipic dihydrazide (**15**) in presence of POCl_3 . (Scheme 6). Variety of disubstituted 1, 3, 4-oxadiazoles have been obtained by using POCl_3 as dehydrating agent.

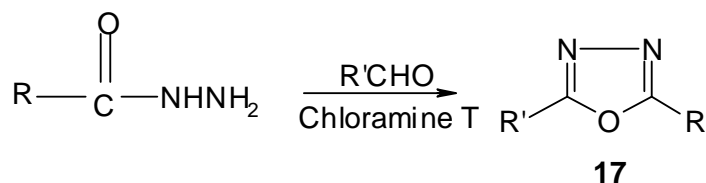


Scheme 5: Synthesis of 2,5-disubstituted 1, 3, 4-oxadiazole by cyclodehydrogenation.



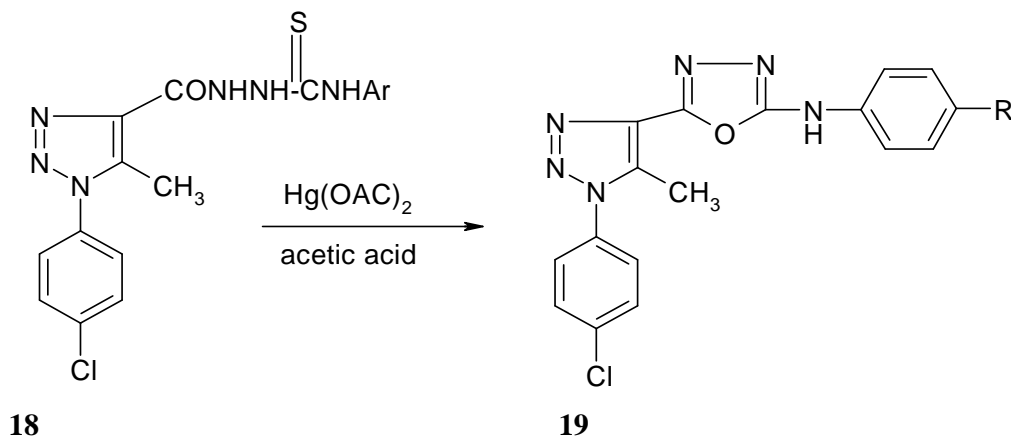
Scheme 6: Synthesis of 1, 3, 4-oxadiazole from semicarbazide

Various oxidizing agents have been employed to obtain 1, 3, 4-oxadiazole derivatives from hydrazides, semicarbazides, thiosemicarbazides and Schiff's bases. S. P. Singh and group [28] reported the synthesis 1, 3, 4-oxadiazole (**17**) through a one pot procedure (**Scheme 7**) involving the reaction of acylhydrazide with aldehydes followed by in-situ cyclization using Chloramine T (p-CH₃-C₆H₄SO₂N⁻Cl Na⁺.3H₂O) as an oxidizing agent. 5-(1-p-chlorophenyl-5-methyl-1, 2, 3 - triazol-4-yl)-2-phenylamino- 1, 3, 4-oxadiazole (**19**) was synthesized from corresponding thiosemicarbazide (**18**) in presence of mercuric acetate as an oxidizing agent [29] (**Scheme 8**).

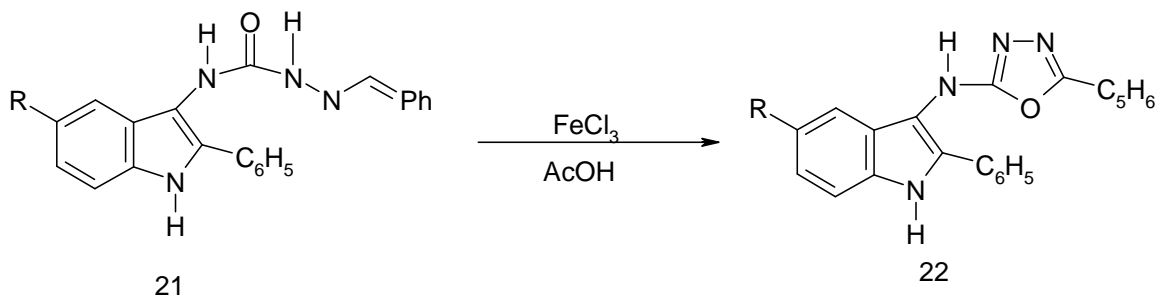


Scheme 7: Synthesis of 1, 3, 4-oxadiazole using Chloramine T

The Schiff's bases of 2-phenyl-3-semicarbazidoindole (**20**) on oxidative cyclo dehydrogenation with ferric chloride in acetic acid gave substituted-3-(5'-phenyl-oxadiazolyl)-aminoindole (**21**) (**Scheme 9**) [30].

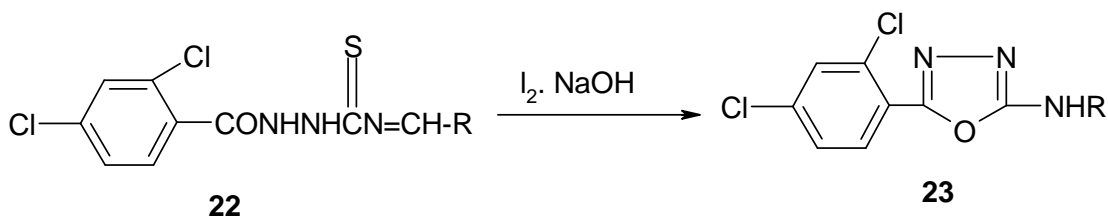


Scheme 8: Synthesis of 1, 3, 4-oxadiazole using mercuric acetate.

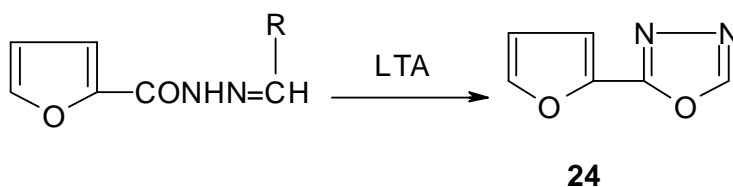


Scheme 9: Synthesis of 1, 3, 4-oxadiazole analogues from Schiff's Bases using FeCl₃

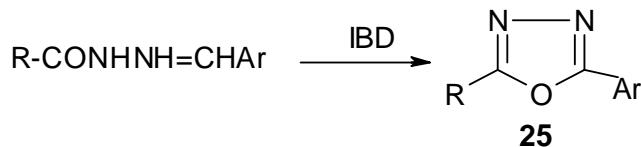
The Schiff's bases of 1-(2, 4-dichlorobenzoyl)-4-phenyl thiosemicarbazide were oxidized by iodine at room temperature in presence of alkali to yield cyclised product (**23**) (**Scheme 10**) [31]. H. Saikochi and coworkers synthesized 5-substituted -2-2-(furyl)-1, 3, 4-oxadiazoles (**24**) using LTA as an effective oxidizing agent (**Scheme 11**) [32]. This method is widely employed for synthesis of 2, 5-disubstituted 1, 3, 4-oxadiazole because of ease in work up and higher yield. Utilization of hypervalent reagent is a green approach in organic synthesis. V. Sharma and colleagues [33] employed hypervalent iodine (IBD) for oxidation of Schiff's base to obtain 2, 5-disubstituted 1, 3, 4-oxadiazole (**25**) (**Scheme 12**).



Scheme 10: Synthesis of 1, 3, 4-oxadiazole analogues using iodine /potassium iodide



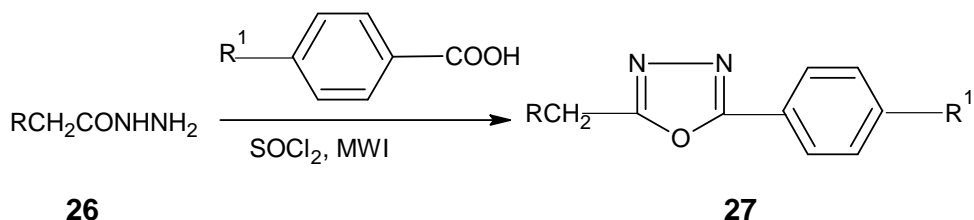
Scheme 11: Synthesis of 1, 3, 4-oxadiazole analogues using lead tetraacetate



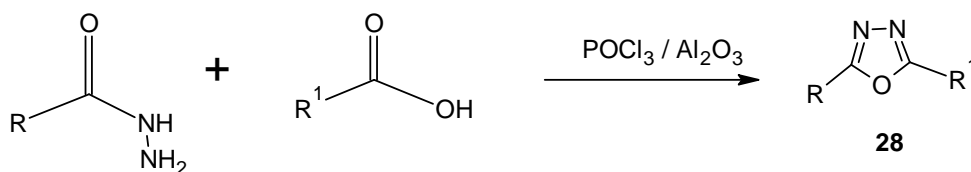
Scheme 12: Synthesis of 1, 3, 4-oxadiazole analogues using hypervalent iodine

Traditionally organic reactions are heated using an external heat source and therefore transferred by conductance. This is comparatively slow and inefficient method for transferring energy into the system because it depends on thermal conductivity of the various material that must be penetrated and results in increasing the temperature of the reaction vessel being higher than that of the reaction mixture. By contrast microwave irradiation produces efficient internal heating by direct coupling of microwave energy with polar molecules. Microwave assisted organic synthesis is mainly based on the efficient heating of materials by microwave dielectric heating effects. Microwave dielectric heating is dependent on the ability of a specific material to absorb microwave energy and convert it to heat [34-35]. In many instances significantly reduced reaction times, high yields and cleaner reaction profiles are being experienced, allowing for more rapid reaction optimization and library synthesis. Solvents with lower boiling points can be used under pressure (closed vessel condition) and be heated at temperatures considerably higher than their boiling point.

Microwave heating allows direct ‘in core’ heating of the reaction mixture, which results in a faster and more even heating of the reaction mixture. M Kidwai and coworkers [36] reported synthesis of disubstituted 1, 3, 4-oxadiazole derivatives (**27**) using mixture of hydrazide, substituted aromatic acids and thionyl chloride under microwave irradiation (MWI) within 6-7 min. (**Scheme 13**). Similarly, Khalid M. Khan and his group [37] reported the microwave assisted synthesis of such diaryl-1, 3, 4-oxadiazoles (**28**). In this a number of commercially available hydrazides were treated with different carboxylic acids in the presence of phosphorus oxychloride to afford the desired products (**Scheme 14**).



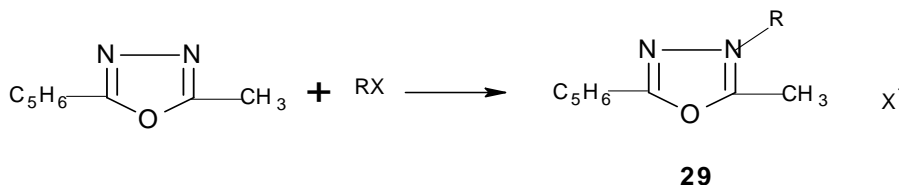
Scheme 13: Synthesis of 1, 3, 4-oxadiazole analogues under Microwaves



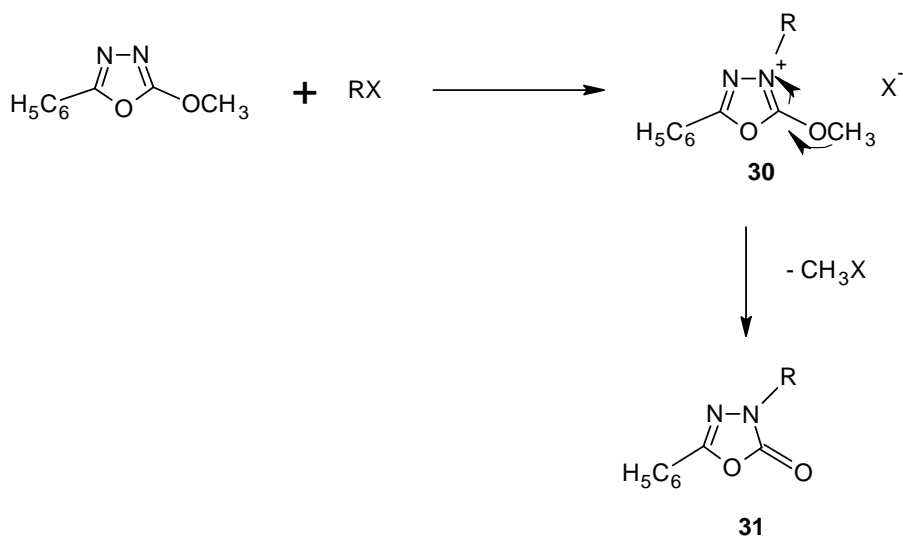
Scheme 14: Synthesis of 1, 3, 4-oxadiazole analogues under Microwave via cyclodehydration.

2.3 Reactions of 1, 3, 4-Oxadiazole

The substituted and unsubstituted 1, 3, 4-oxadiazole undergoes varieties of organic reactions. Due to very low π -electron density on the carbon atom, the attack of electrophile preferentially occurs at the position 3 with the formation of 1, 3, 4 -oxadiazolium salts (**29**) (**Scheme 15**). However, the alkylation of 2-alkoxy-1, 3, 4- oxadiazole with alkyl halides produces labile oxadiazolium salt (**30**) which undergo O-dealkylation to provide 4-alkyl – oxadiazolin- 5-ones (**31**) (**Scheme 16**). 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.

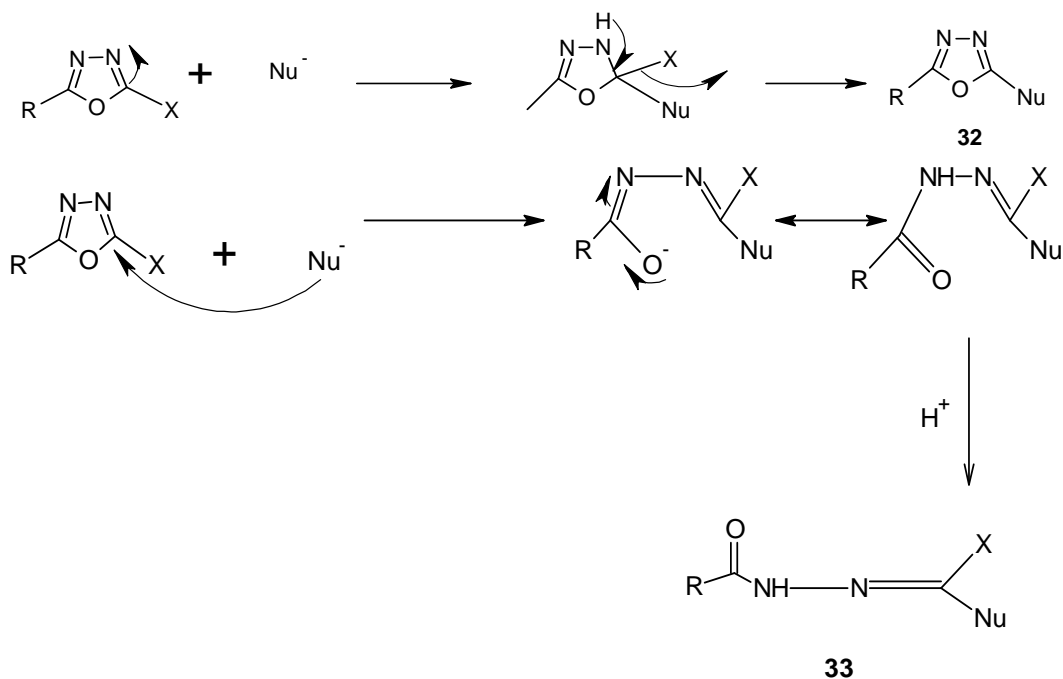


Scheme 15: Attack of electrophiles (R) at 3rd position

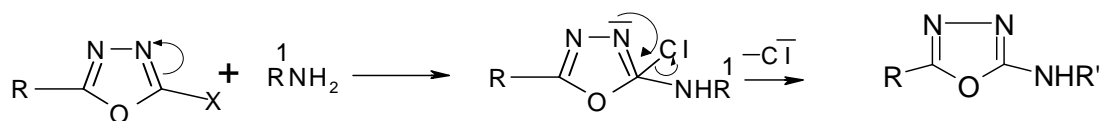


Scheme 16: Mechanism of reaction with electrophiles

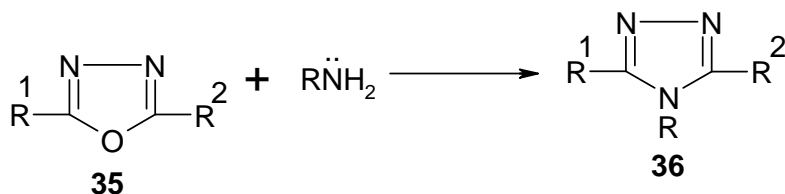
Reactions with nucleophiles are also reported. The carbon atoms in 1, 3, 4 -oxadiazole ring are relatively with low π electron density and therefore attack of nucleophiles occurs at this carbon atom. The reaction proceeds either with nucleophilic substitution (**32**) or with ring cleavage (**33**) (**Scheme 17**). 1, 3, 4-oxadiazole substituted with halogen or sulfonyl group at the position-2 easily undergo nucleophilic substitution reaction. The reaction of 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 (**34**) (**Scheme 18**).



Scheme 17: Nucleophilic substitutions and ring cleavage

**Scheme 18: Reaction with amines**

The reaction of alkyl or aryl- 1, 3, 4-oxadiazoles (**35**) with nucleophile involve the cleavage of 1, 3, 4-oxadiazole ring ending to the formation of hydrazine derivative which may recyclize to form 1, 2, 4 -triazoles (**36**) (**Scheme 19**). Alkyl and aryl-1, 3, 4 -oxadiazole undergo acid or base catalyzed ring opening reaction in aqueous solution with formation of diacylhydrazines. 1, 3, 4 -oxadiazole is thermally stable and the stability of the ring is increased with the substitution of the aryl groups.

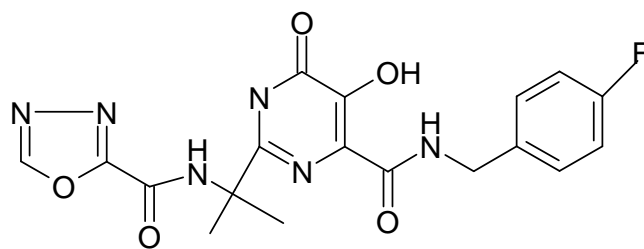
**Scheme 19: Formation of 1,2,4-triazole from 1,3,4-Oxadiazole**

However, 1, 3, 4-oxadiazolin-5-one undergo thermal and photochemical ring opening reaction with the loss of carbon dioxide to provide nitrilimines [40]. It is well documented that diaryl 1, 3, 4-oxadiazole react with benzothiophene leading to formation of oxadiazepine as a major product. But irradiation of this molecule with benzophenone as sensitizer results in (2+2) cycloadduct product. 2, 5 substituted- 1, 3, 4- oxadiazole are greatly affected by strong acid or base. Cleavage of the ring is followed by hydrazine formation. In general aryl derivatives are less sensitive than alkyl substituted derivatives.

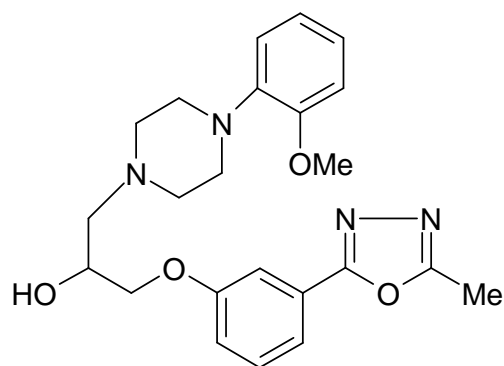
A special type of rearrangement known as ‘Dimroth rearrangement’ is exhibited by 1,3,4-oxadiazole having a substituents containing heteroatom like O,S,N at position 2 or 5 in presence of strong acid or strong alkali upon long duration heating [38]. If it is intended to carry out the reaction involving heteroatom at position 2 or 5 of 1, 3, 4 -oxadiazole, the reaction should be carried out at lower temperature (< 80 °C) after mixing the reagent at room temperature. Otherwise, possibility of Dimroth rearrangement always exists which may yield mixture of both.

3. Biological activity [39]

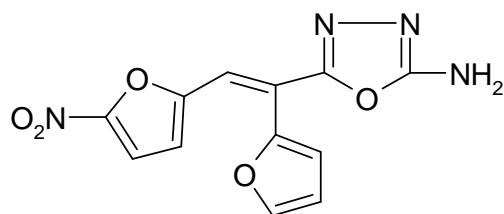
The capacity of 1, 3, 4-oxadiazole nucleus to undergo variety of chemical reaction have made it medicinal backbone on which number of potential molecules can be constructed. A few therapeutic agents were synthesized possessing of 1, 3, 4-oxadiazole nucleus are mentioned below.



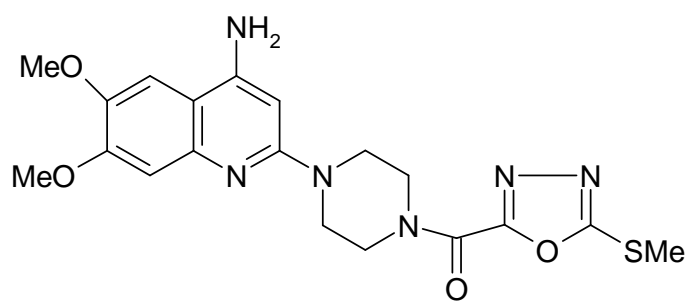
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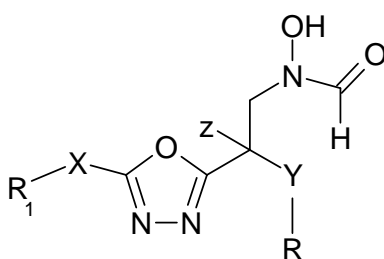
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Raltegravir (**37**) an antiretroviral drug by Merck & Co, is used to treat HIV infection. HIV replication involves the conversion of viral RNA into DNA, which is then incorporated into the host cell genome through a process catalyzed by the HIV integrase enzyme. By blocking integrase, raltegravir inhibits HIV replication. Nesapidil (**38**) is categorized as a Class IV antiarrhythmic drug. It is calcium channel blocker. Its major effect is to slow down Ca⁺² channels. The result is a slowing of AV conduction and sinus rate. Nesapidil causes change in the preload, after load, contractility and coronary blood flow. Furamizole (**39**) a nitrofurantoin derivative possesses a strong antibacterial activity. Tiodazosin (**40**) is an antihypertensive drug.

Under *in vitro* conditions, tiodazosin produced a noncompetitive antagonism of alpha adrenergic receptors in the portal vein, It did not show marked affinity for presynaptic alpha adrenergic receptors and lacked any measurable direct vasodilator effects (nonreceptor mediated) independent of alpha adrenergic receptor blockade. BB-83698 (**41**) is an antibacterial agent. It is an inhibitor of metallo enzyme PDF (Peptide Deformylase). PDF is considered as the most promising bacterial targets in the search for novel mode of action of antibiotics that lacks cross-resistance to existing drugs.

Conclusion

This review thus gives an overview of the various synthetic routes used to form a biologically rich oxadiazole moiety as well as the reactions the molecule undergoes to yield various other important molecules. It also highlights the therapeutic properties of the oxadiazole ring and the availability of varied drugs in the market containing the ring. Thus this paper proves to be significant for further research work on the bioactive oxadiazole ring.

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