 DOI: 10.18231/2394-2797.2017.0010

Synthetic trends followed for the development of 1,3,4-oxadiazole based compounds

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Abstract

1,3,4-oxadiazoles, heterocycles bearing one oxygen and two nitrogen atoms in a five membered ring have their application in the diverse areas of medicine. Enough literature is available demonstrating antibacterial, antifungal, anticonvulsant, antiviral, antidiabetic and antimalarial potential of the moiety. Owing to their wide applications, scientists across the globe are engaged in the design and development of oxadiazole derived medicinal agents. This motif can also be traced in a number of drug molecules. Most commonly adopted method for their synthesis includes he reaction between acid hydrazides and acid chorides/carboxylic acids or direct cyclization of diacylhydrazines in the presence of different dehydrating agents like phosphorus oxychloride, thionyl chloride, phosphorus pentaoxide and polyphosphoric acid. This manuscript covers different conventional and non-conventional approaches adopted for the synthesis of 1,3,4-oxadiazole derivatives.

Keywords: 1,3,4-Oxadiazole, Synthesis, Cyclization Agent, Microwave Assisted Synthesis

Introduction

Oxadiazoles, five membered heteroaromatic rings bearing two carbon, two nitrogen, and one oxygen atom are well known to exist in different regioisomeric forms.[1,2] These regioisomeric forms are shown in **Fig. 1**.This moiety is derived from furan by substitution of two methylene groups with pyridine type nitrogen atoms.[3] 1,3,4-oxadiazole is valued in the field of medicinal chemistry for its low lipophilicity.[4]

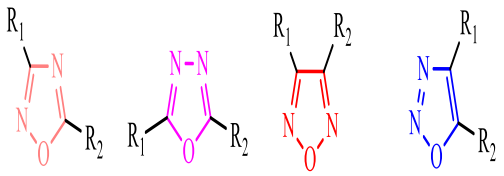


Fig. 1: Regioisomers of Oxadiazole

1,3,4-oxadiazole moiety is known to elicit different pharmacological activities[5,6] like anticancer,[7] antiviral,[8] antibacterial,[9] antifungal,[10] antidiabetic,[11] antioxidant,[12] antimalarial,[13] analgesic and anti-inflammatory,[14]etc. This motif is frequently traced in a number of drug molecules[15] shown in **Fig. 2**. Raltegravir is an antireteroviral drug with 1,3,4-oxadizole.[16] 1,3,4-oxadiazole bearing furamizole is an antibacterial agent.[17] 1,3,4-oxadiazole bearing drugs, nedsapidil and tiodazosin elicit their action as antihypertensive agents.[18] Zibotentan belongs to the category of anticancer agents.[19]

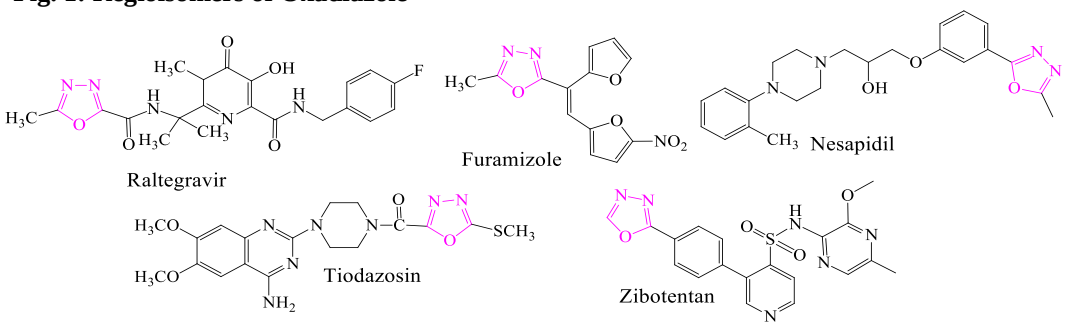


Fig. 2: Drug molecules bearing 1,3,4-Oxadiazole

Most common synthetic procedure for laboratory preparation of 1,3,4-oxadiazole based compounds is cyclodehydration of acid and hydrazide in the presence of dehydrants such as phosphorus oxychloride, trifluoroacetic anhydride, thionyl chloride, polyphosphoric acid.[20,21] Mechanism for the same is shown in **Fig. 3**.

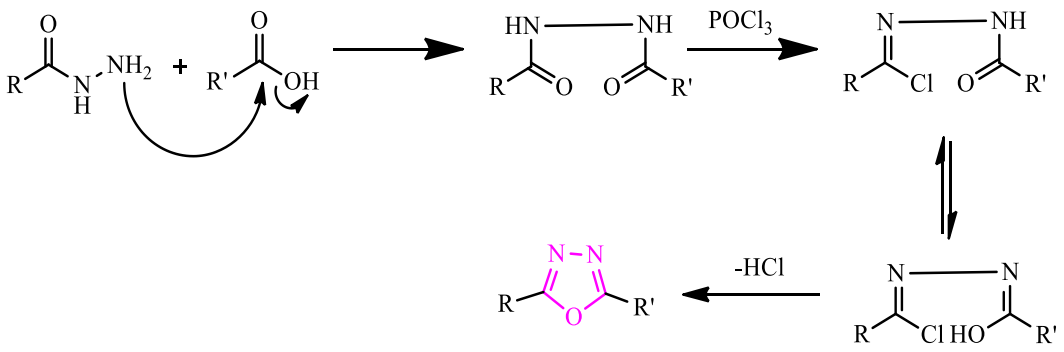


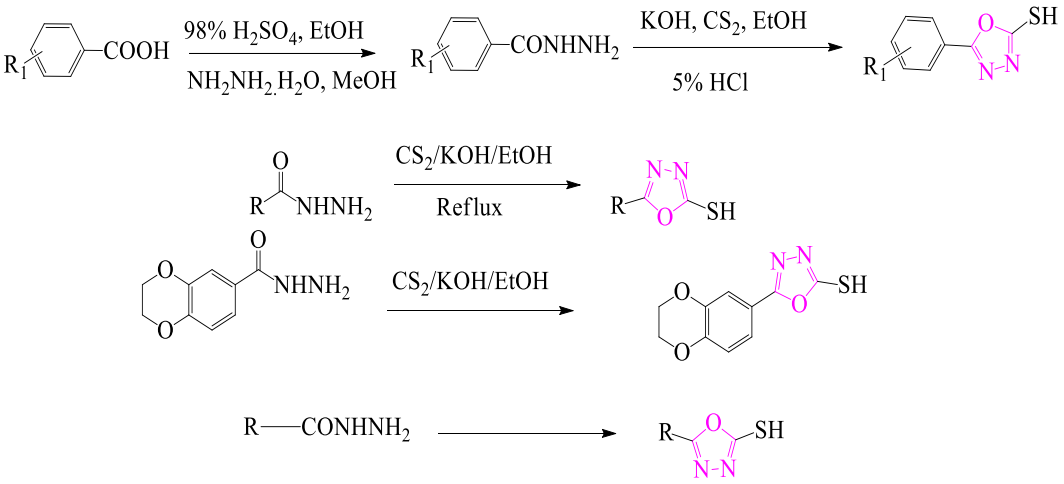
Fig. 3: Mechanism for synthesis of 1,3,4-Oxadiazole

Chemistry of the Ring: This ring is known to behave as a weak base. Presence of two pyridine type nitrogen atoms leads to reduction in aromaticity of the ring to such an extent, that it behaves as a conjugated diene. Owing to relatively low electron density on carbon atom, electrophilic substitution reactions are very difficult at the carbon atom. This low electron density on carbon atom is due to electron withdrawal nature of pyridine type nitrogen atoms.[22,23]

Trends in Synthesis: In spite of the conventional dehydration in the presence of dehydrating agent, there are several other methods which are being used by researchers. Such different methods have been mentioned in the subsequent text.

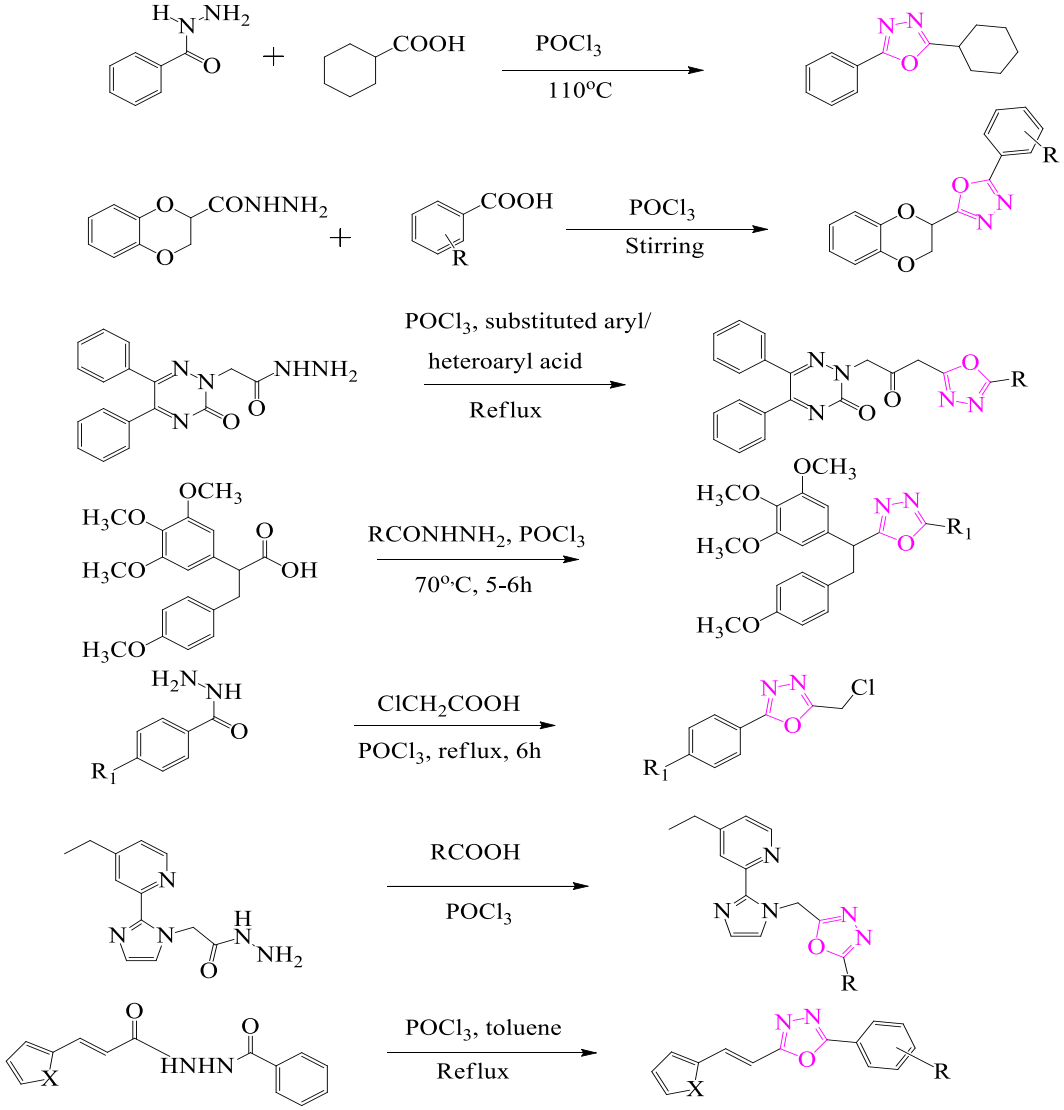
Synthesis in the Presence of a Base: Wang *et al.* synthesized 1-aryl-4-hydroxy-1*H*-pyrrol-2(5*H*)-one derivatives and assessed their bioactivities. For synthesizing the desired compounds, presence of a base was required. KOH was used in this case.[24] Ahmed *et al.* also prepared a series of 1,3,4-oxadiazoles in the presence of base.[25] Sun and co-workers employed basic conditions forsynthesis of 1,3,4-oxadiazole-2(3*H*)-thione derivatives targeting focal adhesion kinase.[26] Li *et al.* had developed a series of 1,3,4-oxadiazole derivatives and evaluated them for antibacterial activity against rice bacterial leaf blight and tomato bacterial wilt under basic conditions.[27] An overview is shown in **Scheme 1**.

Scheme 1: Formation of 1,3,4-Oxadiazole in the presence of KOH



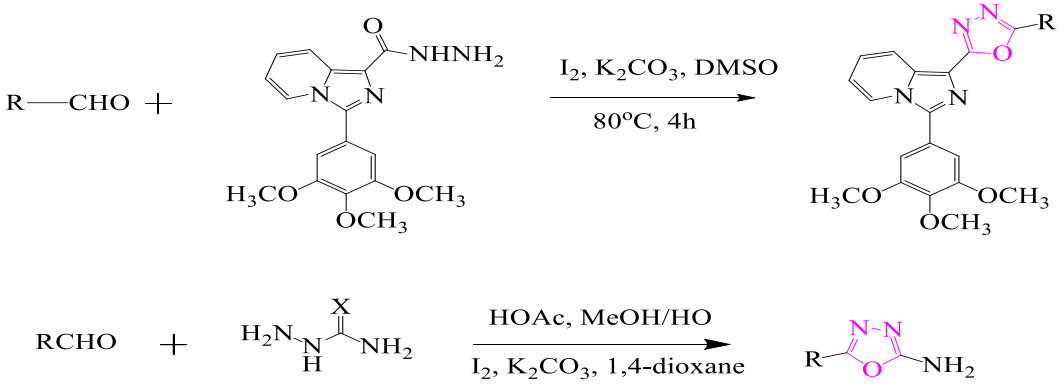
Synthesis in the presence of $POCl_3$: In an effort towards synthesizing 2,5-substituted-1,3,4-oxadiazole derivatives, Selvaraj and co-workers used $POCl_3$ as the cyclization agent. These candidates were screened for their antidiabetic, anti-inflammatory and anticancer potential.[28]Khalilullah and co-workers synthesized a series of 1,3,4-oxadiazole derivatives bearing 1,4-benzodioxane ring using $POCl_3$. These were evaluated for antimicrobial activity.[29] 1,3,4-oxadiazole derivatives prepared by Banerjee *et al.* using $POCl_3$ were tested for anti-inflammatory and analgesic activities.[30] Kamal and co-workers developed a series of combretastatin linked 1,3,4-oxadiazole conjugates as potential tubulin polymerization inhibitors.[31] El-Din *et al.* also used $POCl_3$ to synthesize 1,3,4-oxadiazole derivatives possessing sulfonamide moiety.[32] Wani and co-workers developed a series of 2-(4-ethyl-2-pyridyl)-1*H*-imidazole which was clubbed with 1,3,4-oxadiazole using $POCl_3$ as the cyclization agent.[33]Kudelko and Wroblowska reported synthesis of 1,3,4-oxadiazole derivatives in the presence of $POCl_3$, taking toluene as the solvent.[34] Overview of these reactions is given in **Scheme 2**.

Scheme 2: Synthesis in the presence of $POCl_3$



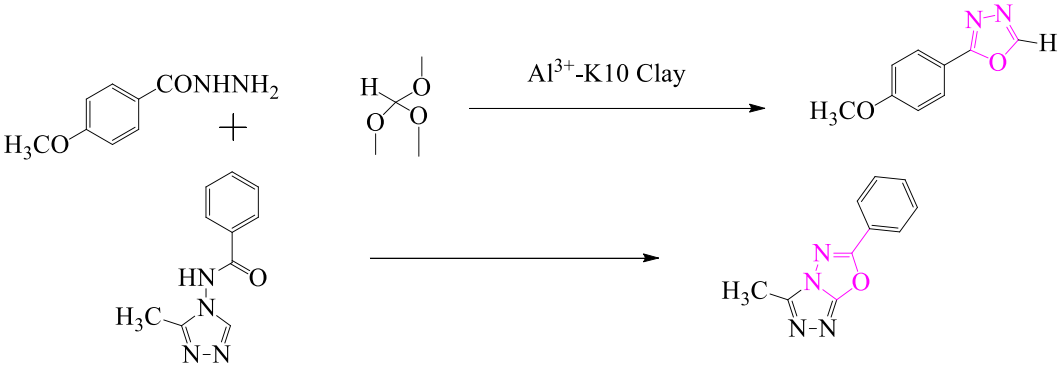
Iodine Mediated Synthesis: A series of imidazopyridinyl-1,3,4-oxadiazole was synthesized by Rao *et al.* in the presence of I_2, K_2CO_3 in DMSO These agents were screened for cytotoxic effects.[35]Niu and co-workers also reported a method for synthesis of 2-amino-1,3,4-oxadiazoles in the presence of iodine.[36]These reactions are shown in **Scheme 3**.

Scheme 3: Iodine mediated synthesis of 1,3,4-oxadiazole



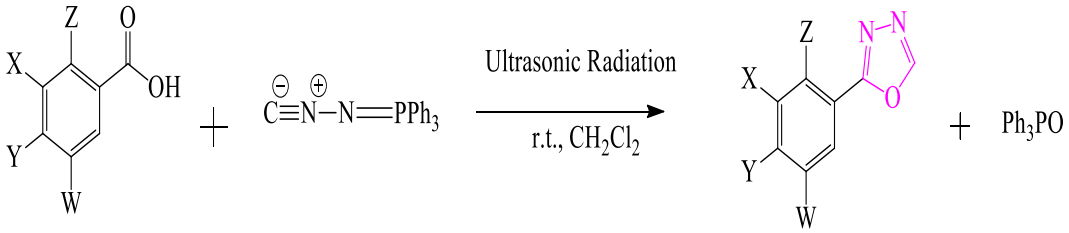
Microwave Assisted Synthesis: Al^{3+}-K10 montmorillonite clay served as a heterogeneous catalyst for the synthesis of 1,3,4-oxadiazoles under microwave irradiation.[37] Breuni*g et al.* reported microwave accelerated synthesis of 1,3,4-oxadiazole derivatives.[38] Overview of microwave assisted reactions is given in **Scheme 4**.

Scheme 4: Microwave assisted synthesis of 1,3,4-Oxadiazoles



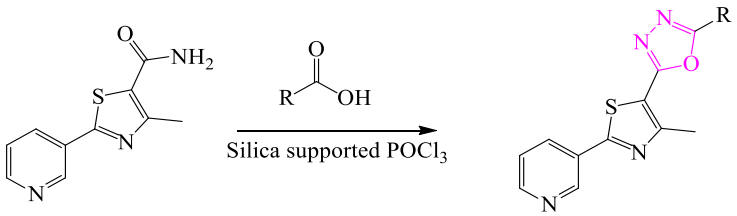
Sonochemical Synthesis: Rouhani and co-workers reported ultrasound promoted synthesis of 2-aryl-1,3,4-oxadiazoles at ambient temperature,[39] shown in **Scheme 5**.

Scheme 5: Ultrasound mediated synthesis of 1,3,4-Oxadiazoles



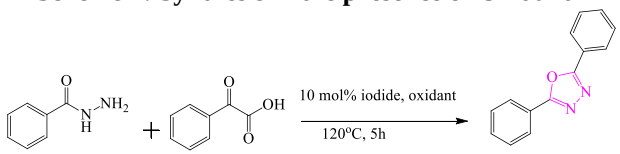
Silica Supported $POCl_3$: Pyridinyl substituted thiazolyl acid hydrazide was condensed with benzoic acids/nicotinic acids in the presence of silica supported $POCl_3$ to yield 1,3,4-oxadiazole derivatives,[40] shown in **Scheme 6**.

Scheme 6: Synthesis of 1,3,4-Oxadiazole on silica supported $POCl_3$



Synthesis in the presence of oxidant: This sort of synthesis was reported by Gao *et al.* Reaction conditions involved presence of 10 mol% iodide, 1.2 equiv. base and 4 equiv oxidant in solvent at 120˚C for 5 h.[41] This reaction is shown in **Scheme 7**.

Scheme 7: Synthesis in the presence of Oxidant



Conclusion

1,3,4-oxadiazoles find their significant place in the field of drug discovery and development. This drives the interest of different scientists for development of novel methods for synthesis of novel oxadiazole. Cyclization in the presence of $POCl_3$ is the most conventional method adopted by researchers. However, a few alternative methods like ultrasonic or microwave irradiation have also been reported in the manuscript.

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