VARIOUS APPROACHES FOR SYNTHESIS OF OXADIAZOLE DERIVATIVES
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ABSTRACT
Oxadiazole, a five-membered heterocycle having two carbon atoms, two nitrogen atoms, one oxygen atom, and two double bonds, inclusive of inductive effect & having efficient anticancer, antifungal, antimicrobial, insecticidal, anti-allergic activity etc... The presence of heterocyclic structures exerts various physiologic effects on the body. In the present study we have reviewed several newer approaches of synthesizing the substituted oxadiazole derivatives via catalytic reaction & by the application of various suitable reagents.

KEYWORDS: (Oxadiazole, Nucleophilic & Electrophilic reactions in Oxadiazole, Parallel Synthesis, One-pot synthesis, 1, 3, 4-Oxadiazolylphenylene derivatives, Anti-cancer activity)

INTRODUCTION
Oxadiazole is a five-membered heterocycle having two carbon atoms, two nitrogen atoms, one oxygen atom, and two double bonds1.

Oxadiazole is an important heterocyclic ring present in variety of biologically active molecules inclusive of fungicidal, bactericidal, anticancer, antitubercular activities, etc2.

Oxadiazole moiety is derived from furan by replacing two -CH= group with 2 pyridine typed nitrogen (-N=). So there should be possibility of 4 oxadiazole isomers reliant on the nitrogen atom position in the ring as follows3.

Isomers Of Oxadiazole

Basic Information
Oxadiazole is a heterocyclic nucleus which gains heavy interest by many research scholars regarding inventions of novel remedial molecules. There are possibly 4 isomers of oxadiazoles in which 1, 3, 4-oxadiazole have enormous importance. Variety of therapeutically active agents e.g. raltagravir as HIV-integrase inhibitor, furamizole as nitrofuran antibacterial, antihypertensive agents nesapidal, anti-microbial, anticancer activity etc. are based on 1,3,4-oxadiazole moiety. The 1, 3, 4-oxadiazole exhibit variety of reactions such as electrophilic substitution, nucleophilic substitution, thermal and photochemical reactions3.
Chemical Features of Oxadiazole Moiety

Oxadiazole is a very weak base because there is an inductive effect of extra heteroatom. As we know, Oxadiazole consists of the 2 pyridine type nitrogen (-N=), hence reduction in aromaticity of oxadiazole ring and which in turn leads the oxadiazole ring to exhibit the conjugated diene character.

There is no or very less scope of electrophillic substitutions at the carbon atom in oxadiazole ring due to less electron density on the same carbon atom. Rather, electrophillic attack can occurs at nitrogen, but again there must be association of electron-releasing groups in oxadiazole ring.

Whereas for Nucleophilic substitution like in Halogen-substituted oxadiazole there is replacement of halogen atom by nucleophiles

Brief Descriptions on Reactions of Oxadiazole

A). Reactions with electrophile

If we see the reaction below it proves that, because of low \( \pi \)-electron density on the carbon atom, electrophile attacks favorably at 3\(^{\text{rd}}\) position and results in 1,3,4-oxadiazolium salts as follows.

B). Reactions with Nucleophile

Now, in case of Nucleophiles the carbon atoms in 1, 3, 4-oxadiazole ring have low \( \pi \) electron density which gain access to the attack of nucleophiles on this carbon atom and reveals that the reaction progress either with substitution of nucleophile or cleavage of ring. The halogen or sulfonyl group substituted 1, 3, 4-oxadiazole moiety at 2\(^{\text{nd}}\) position can easily endure nucleophilic substitution reaction.
Literature review for various synthetic approaches

One-pot synthesis of 1, 2, 4-oxadiazoles using carboxylic acid esters with amidoxime implementing potassium carbonate and eventually reflux for 6-12 hrs.

Scheme-1

\[
\begin{align*}
R^1 \quad \text{O} \\
\quad \text{O} \\
\quad \text{R}^2 \\
\quad \text{R}
\end{align*}
\]

\[+\]

\[
\begin{align*}
\text{N} \\
\text{O} \\
\text{H} \quad \text{R}^2 \\
\text{amines}
\end{align*}
\]

\[
\xrightarrow{\text{K}_2\text{CO}_3, \text{toluene reflux, 6-12 hrs}}
\]

\[
\begin{align*}
\text{R}^1 \\
\text{O} \\
\text{N} \\
\text{R}^2
\end{align*}
\]

\[R = \text{Me, Et}\]

Scheme-2

Parallel synthetic approach of 1, 2, 4-oxadiazoles implementing CDI activation.

Scheme-3

Step: 1 Solvent-free microwave-assisted synthesis of oxadiazole containing imidazole moiety.

\[
\begin{align*}
\text{N} \\
\text{O} \\
\text{H}
\end{align*}
\]

\[
\begin{align*}
\text{N} \\
\text{C} \quad \text{H} \quad 3 \\
\text{C} \quad \text{H} \\
\text{C} \quad \text{O}
\end{align*}
\]

\[\xrightarrow{\text{ClCH}_2\text{CO}_2\text{C}_2\text{H}_5} \]

\[\xrightarrow{\text{K}_2\text{CO}_3, \Delta} \]

\[\text{EtOH, } \Delta \]

\[\text{N}_2\text{H}_4\text{H}_2\text{O} \]

\[
\begin{align*}
\text{N} \\
\text{CH}_2\text{CONHNH}_2
\end{align*}
\]

Step: 2

\[
\begin{align*}
\text{N} \\
\text{O}_2 \\
\text{N}
\end{align*}
\]

\[
\begin{align*}
\text{N} \\
\text{O}_2 \\
\text{N}
\end{align*}
\]

\[\xrightarrow{\text{POCl}_3, \text{MW}} \]

\[\xrightarrow{\text{POCl}_3, \Delta} \]

\[
\begin{align*}
\text{O} \\
\text{R}
\end{align*}
\]
where $R = a$: C$_6$H$_5$; b: 4-CH$_3$C$_6$H$_5$; c: 4-OCH$_3$C$_6$H$_4$; d: 4-ClC$_6$H$_4$; e: 2-CH$_3$C$_6$H$_4$; f: C$_5$H$_4$N; g: 2-C$_4$H$_3$O; h: C$_6$H$_5$-OCH$_2$; i: 4-CH$_3$-C$_6$H$_4$-OCH$_2$; j: 2-CH$_3$-C$_6$H$_4$-OCH$_2$; k: 4-Cl-C$_6$H$_4$-OCH$_2$.

Scheme 4
Synthesis of 6-Methyl-4-aryl-5-(5-phenyl-1,3,4-oxadiazol-2-yl)-1,2,3,4-tetrahydropyrimidine-2(1H)-one having efficient antibacterial activity.$^2$

Scheme 5
Swift Synthesis of 1, 2, 4-Oxadiazoles employing Polymer-Supported Reagents in Microwave Heating. 1, 2, 4-Oxadiazoles swiftly be synthesized from a range of carboxylic acids & amidoxime by implementing either of two method A & B given below, which results in elevated yields.$^7$
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Method A:
HBTU, PS-BEMP, CH₃CN
MW, 160°C, 15 min

R = Aryl or Alkyl

Method B:
1). PS-PPh₃, CCl₃CN
MW, 100°C, 5 min
2). DIEA, THF
MW, 150°C, 15 min

77%-99% yield

Scheme-6
An upgraded oxadiazole synthesis implementing peptide coupling reagents:
Synthesis of substituted 1,2,4-oxadiazoles in elevated yields in one pot method by condensing analogous amidoxime with carboxylic acids in the occurrence of peptide coupling reagent in diglyme & to heat the reaction mixture at about 100°C for numerous hours.

Scheme-7
Synthesis of some 3- [5-(6-methyl-4-aryl-2-oxo-1, 2, 3, 4-tetrahydropyrimidin-5-yl)–1, 3, 4-oxadiazol-2-yl]-imino -1, 3-dihydro-2H-indol-2-one derivatives.

Where:
Ar = a:C₆H₅, b: 2-ClC₆H₄, c: 2,4-(Cl)₂-C₆H₃, d: 3,4,5-(OCH₃)₃-C₆H₂,
e: 4-CH(CH₃)₂-C₆H₄, f: 4-F-C₆H₄, h: 3-OH-4-OCH₃-C₆H₃, i: 4-N(CH₃)-C₆H₄
Step: 1

\[
\begin{align*}
\text{Step: 1} & \\
\text{[a-d]} & \\
\text{conc. HCl} & \\
\text{conc. H}_{2}\text{SO}_4 & \\
\text{NH}_2\text{NH}_2 & \\
\end{align*}
\]

\[
\begin{align*}
\text{Step: 2} & \\
\end{align*}
\]
Scheme-8
Synthesis of 1, 3, 4-Oxadiazoles Having Phenol or Thiophenol Group. 

\[ \text{MeSO}_2\text{H / toluene} \]
\[ \text{RCOCI or } \text{Ac}_2\text{O} \]
\[ \text{reflux 2-4 hrs} \]

Where: X = a: O; b: S

Scheme-9
The synthesis of 2-mercapto-5-aryl-1, 3, 4-oxadiazone (2) from well substituted acid hydrazide (1) in presence of CS$_2$/KOH in alkaline media. 

\[ \text{R—CONHNH}_2 \]
\[ \text{CS}_2 / \text{KOH} \]

(1) 
(2)
Scheme-10
Synthesis of 1, 3, 4-Oxadiazolylphenylene derivatives having Anti-cancer activity\textsuperscript{11}.

\[
\text{H}_2\text{NNN} - \text{O} - \text{Cl} - \text{O} - \text{CONNH}_2 \quad \xrightarrow{\text{CS}_2, \text{KOH} \atop 8^\circ \text{C}, 6\text{hr}} \quad \xrightarrow{\text{RCO}_2\text{H}, \text{POCl}_3 \atop 110-20^\circ \text{C}, 6\text{hr}} \quad \text{N} - \text{N} - \text{O} - \text{SH} - \text{N} - \text{N} - \text{R}
\]

Where \( R = \)
\[ 4\text{-ClC}_6\text{H}_4; 4\text{-NO}_2\text{C}_6\text{H}_4; 4\text{-ClC}_6\text{H}_4\text{OCH}_2; 2,4\text{-ClC}_6\text{H}_5\text{OCH}_2; \text{C}_6\text{H}_5\text{NHCH}_2; 4\text{-ClC}_6\text{H}_4\text{NHCH}_2 \]

Scheme-11
Preparation of 1, 3, 4-oxadiazole implementing mercuric acetate\textsuperscript{3}.

Scheme-12
Preparation of 1, 3, 4-oxadiazole amine using cyanogen bromide, which is very easy to apply, takes lesser time & also having better yields\textsuperscript{3}.
Scheme-13
Synthesis of 1, 3, 4-oxadiazole correspondence from Schiff’s Bases using FeCl₃.

![Scheme-13](image)

Scheme-15
Iniminophosphorane-facilitated one-pot synthesis of 1, 3, 4-oxadiazole derivatives (Preparation of 2-aryl-1, 3, 4-oxadiazoles from 4-substituted benzoic acids).

![Scheme-15](image)

where X = I; CN; CO₂Me; OAc; Et

REFERENCES