Review Article

# Synthesis of Oxadiazole Derivatives: An Overview

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**ABSTRACT**

Heterocyclic compounds are of wide interest in all fields due to their wide range of functionalities. Oxadiazole is a heteromoiety which is being reviewed by a number of chemists worldwide in the synthesis of new therapeutically active molecules. A series of methods have evolved for the synthesis of these agents. Out of these a few methods have been reviewed in the present article.

**Keywords:** 1,3,4-oxadiazole, conventional and microwave synthesis, heteroaromatic ring, Schiff base, synthesis methods.

## INTRODUCTION

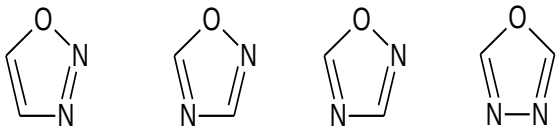
Heteroaromatic ring systems form the pivotal part of many biologically active drug molecules. Heteroaromatic rings are of wide importance as they possess structural similarity with many of biological moieties present in human body like nucleic acids, hormones, neurotransmitters, etc.

Among the many heterocyclics, a number of pharmaceutical products constitute oxadiazoles as the major drug component.

Oxadiazoles are cyclic compounds with one oxygen, two nitrogen and two carbon atoms.

These compounds were termed as 'furodiazoles' in the ancient literatures.

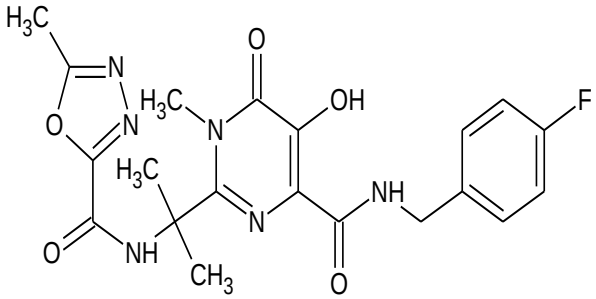
Oxadiazoles exist in four isomeric forms: 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole and 1,3,4-oxadiazole. Of these, 1,3,4-oxadiazoles are widely used in the pharmaceutical field.[1]



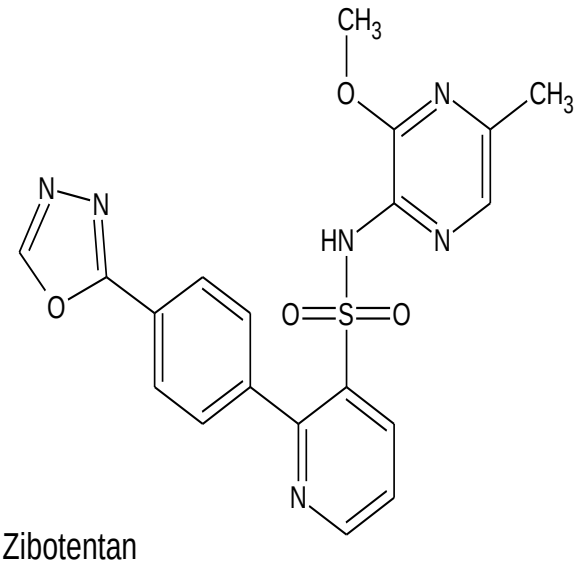
Compounds with 1,3,4-oxadiazole nucleus possess a number of activities like anticancer, antimicrobial, antioxidant, analgesic, antiviral, antihypertensive, anti diabetic and anticonvulsant properties. These compounds are also active against bacteria and fungi.

Oxadiazoles have also gained interest among medicinal chemists by acting as substitutes for many functional groups like carboxylic acids, carboxamides and esters.[2] 1,3,4-oxadiazole moiety containing compounds which are presently in clinical use are: an anti retroviral agent - Raltegravir®[3] and an anticancer agent - Zibotentan®.[4]

Raltegravir and Zibotentan possess the following structures:



Raltegravir



Zibotentan

Derivatives of 1,3,4-oxadiazole comprise a major class of heteroaromatic compounds with versatile pharmacological actions.[5]

Derivatives of 1,3,4-oxadiazole are of wide concern in pharmaceutical field, which is further evidenced by the rapid increase in the count of publications and patents during the former times, about twelve years ago.[6]

Most commonly reported among these activities were: CNS depressants[7], muscular relaxants[8], pain killers[9], herbicidal[10], hypoglycemic[11], antifungal[12], anti-inflammatory[13] and antibacterial activities.[14] In addition, derivatives of 1,3,4-oxadiazole are used in agriculture[15], photosensitizer[16] and liquid crystals.[17]

The derivatives of heterocyclic compounds were also analysed to study their effects on the activities of certain transferase enzymes.

Two scientists, Dere and Polat in 2001 studied the biochemical analysis of (PQ) (1,1-dimethyl-4,40-bipiridillium) on few transferase enzymes and found some alterations (increase or decrease) in the enzyme activities.[18]

1,3,4-oxadiazole nuclei are also known to have unique antiedema, anti-inflammatory[19-21] and anti-hepatitis B viral activities.[22]

The studies on the synthesis of 1,3,4-oxadiazole moieties and identification of their properties has been widely revised during the past two decades in search of newer therapeutically active agents.[23]

The emerging risks of fungal and bacterial resistance to the existing antibiotics has many a times posed serious medical problems during the treatment of pathogenic infections.

However the use of five-membered heterocyclic drugs has proved to be effective in many circumstances.

Nitrogen and oxygen containing five membered azoles are important bioactive agents, due to their vast pharmaceutical and industrial applications.

The activity of azo linkage in 1,3,4-oxadiazoles has also been shown to increase with the incorporation of a suitable heteroaromatic moiety.

Heterocyclic azo compounds are well known for their use as antineoplastics[24], antidiabetics[25], antiseptics[26], and other useful chemotherapeutic agents.[27-28]

1,2,3-Oxadiazoles also play a major role by acting as HIV integrase inhibitors.[29]

Hence the synthesis of such heterocyclic compounds is of wide pharmaceutical significance and a foremost task for chemists.

The common approaches to synthesize oxadiazoles[30] comprise the cyclization reaction of diacylhydrazines.

Alternatively they can be prepared by the reaction of carboxylic hydrazides with keteneylidene triphenylphosphorane[31] (Loffler and Schobert, 1997) or base-catalysed cyclization of trichloroacetic acid hydrazones.[32]

Microwave-assisted synthesis[33-34] has become an important method nowadays that can be used to carry out a wide range of reactions within short time period and with high yields than those obtained with conventional techniques.

The reactions which are not possible under conventional conditions can sometimes be effectively achieved by the high energy of microwave irradiation.[35]

A few synthetic approaches are underlined below:

**Scheme 1**

**Synthesis of 5-beta-[(N-benzene sulphonyl/tosyl)-4-un(substituted anilino]ethyl—mercapto-1, 3, 4-oxadiazoles(4a-f)**

General method of preparation of 5-beta-[(N-benzene sulphonyl/tosyl)-4-un(substituted anilino]ethyl—mercapto-1, 3, 4-oxadiazoles(4a-f), involved the addition of 2.43g(0.02 mole) of carbon disulphide in a dropwise manner to a clear solution of 1.12 g(0.02 mole) of potassium hydroxide in 10 ml of water and 0.02 mole of beta-[(N-benzenesulphonyl/tosyl)-4-(un)substituted aniline]propionic acid hydrazide (3a-f) in 15 ml ethanol with continuous stirring and then cooling in an ice bath.

The mixture was refluxed for 8 hours and then concentrated in vacuo, residual mass poured on crushed ice and then acetic acid was added for neutralization.

The precipitated substance was separated and crystallized from ethanol.[36]

**Scheme 2**

**Synthesis of a novel series of 2-{5-[4-(1-aza-2-(2-thienyl)vinyl)phenyl]1,3,4-oxadiazol-2-ylthio)}-N-arylacetamides**

The procedure involved the cyclisation of N-amino(4-aminophenyl)carboxamide.

A mixture of 0.1 mole of the above compound, 0.01 mole of potassium hydroxide, 0.01 mole of carbon disulfide and 20 ml ethanol was refluxed, cooled and then added to a few ml of cold water which was followed by neutralization with dilute hydrochloric acid.

The solid thus precipitated was collected and recrystallized from ethanol. 0.1 mole of the resulting compound was then dissolved in 75 mL ethanol.

0.1 mole of thiophene-2-carbaldehyde was added in a dropwise manner and boiled for 5 hours.

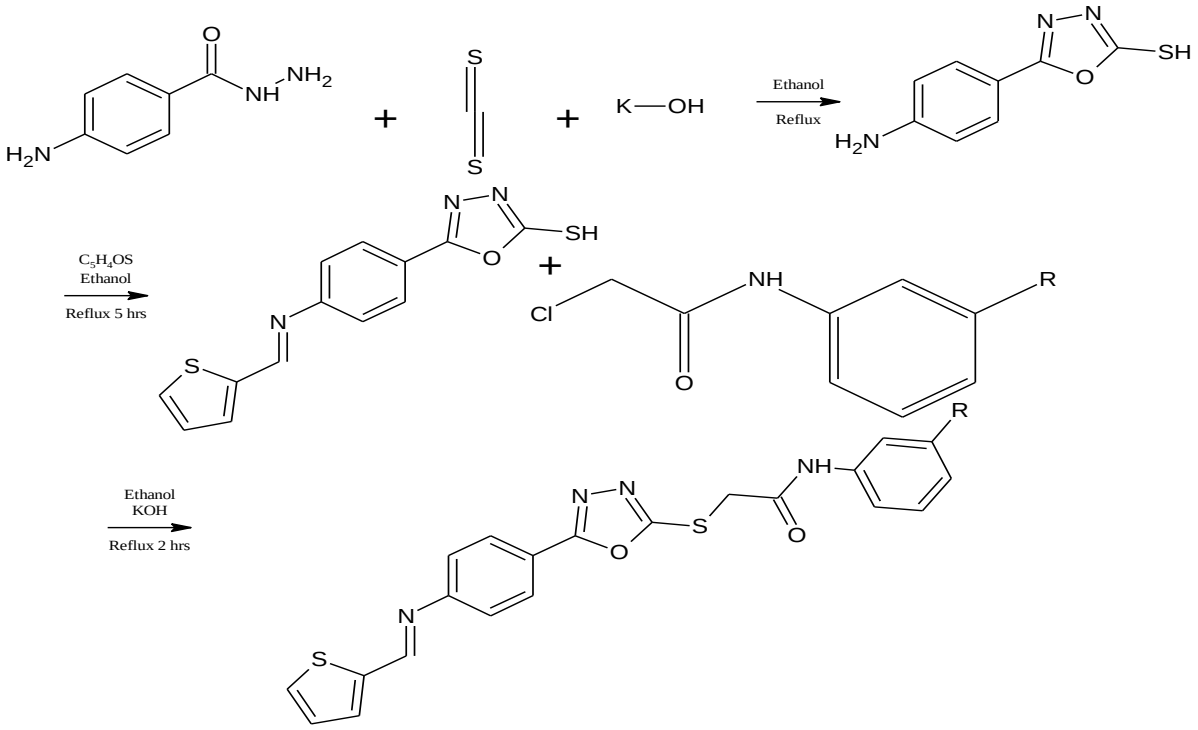
The resulting product was filtered and recrystallized.

About 0.01 mole of the obtained product was dissolved in an aqueous solution of 25% potassium hydroxide in a round bottom flask.

The mixture was subjected to heat (80°C) followed by the addition of various substituted alpha-chloro acetanilide (0.015 mole) in 10 mL ethanol with constant stirring. Again refluxed for 2 hrs.

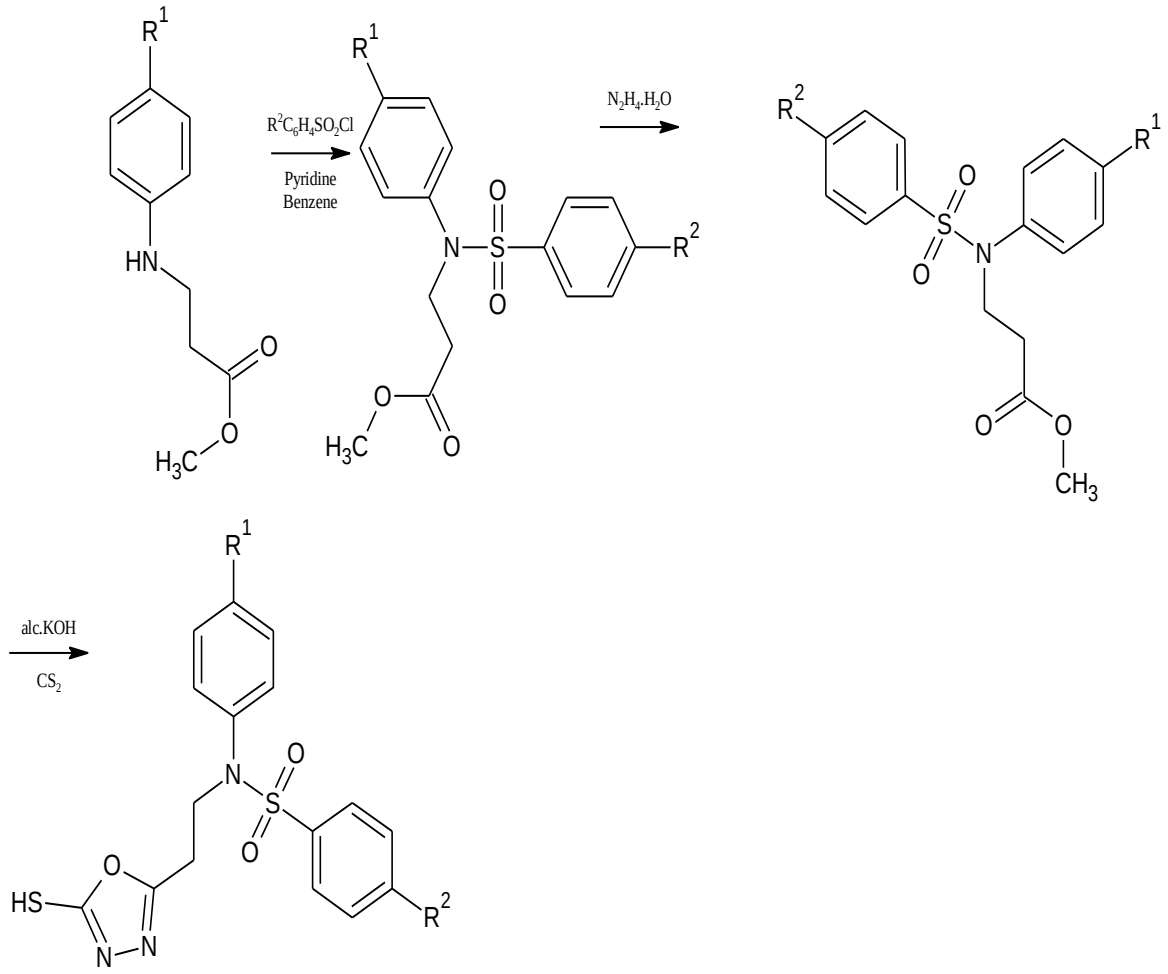
The contents were left overnight.

The crystals formed were separated and then recrystallized using ethyl alcohol.[37]



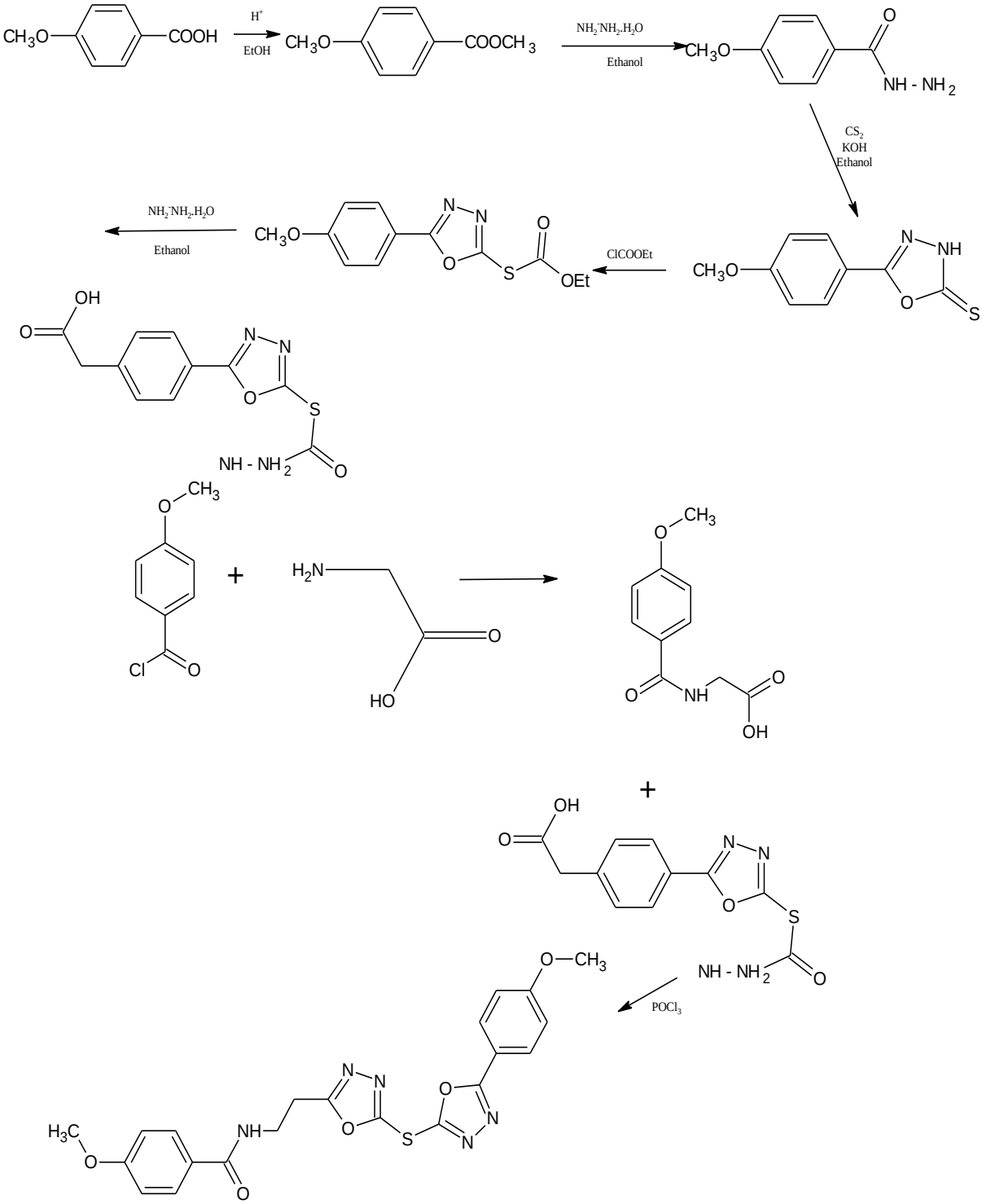

R - 2-Cl, 2-$NO_2$, 2-$CH_3$, 2,4-$(CH_3)_2$, 3-$OCH_3$, 3,4-$(Cl)_2$, 4-F, 4-Br, 4-Cl, 4-$NO_2$, 4-$OCH_3$

**Scheme 1**

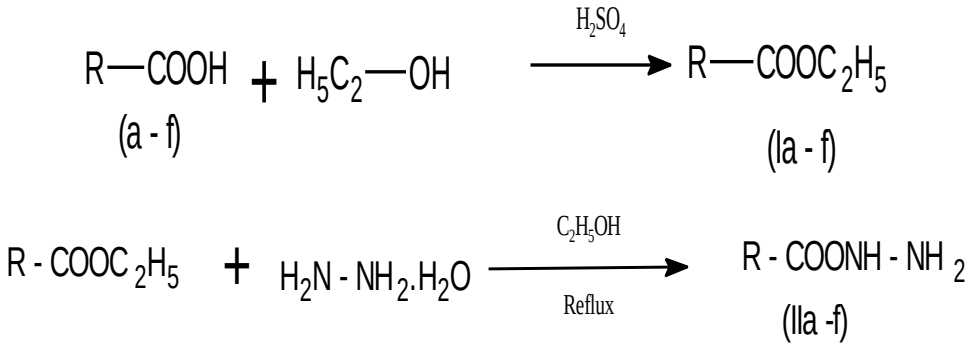


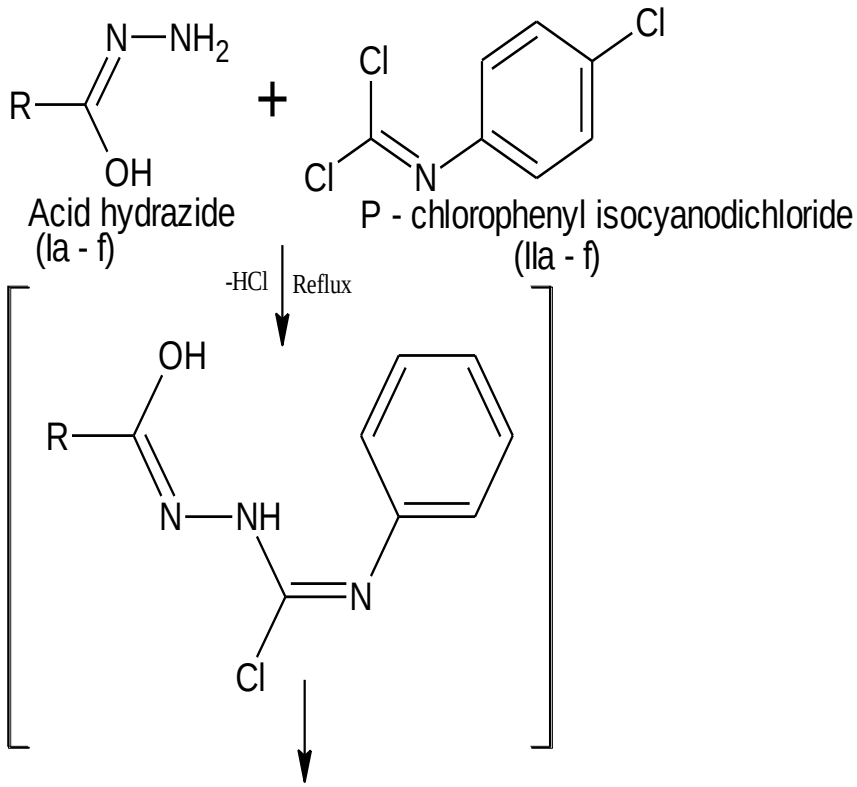

$R^1$: H, $CH_3$, Cl and $R^2$: H, $CH_3$

**Scheme 2**



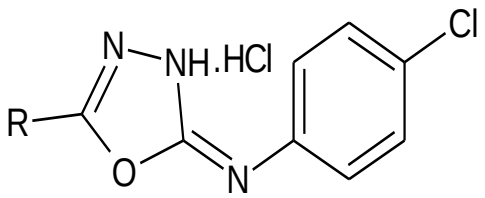
**Scheme 3**






Acid hydrazide (Ia - f)

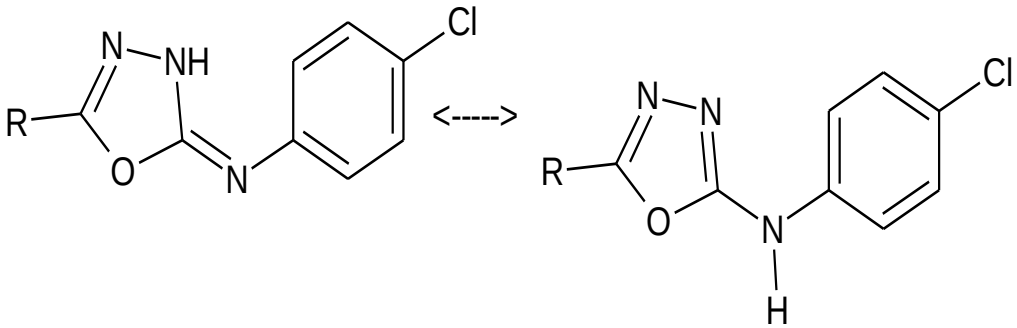
P - chlorophenyl isocyanodichloride (IIa - f)




4 - chloro - N -[ (2E) - 5 -aryl - 1,3,4 - oxadiazol - 2 - ylidene]aniline hydrochloride

(IIIa - f)

dil $NH_4OH$




N - (4 - chlorophenyl) - 5 - aryl - 1,3,4 - oxadiazol - 2 - amine

(IVa - f)

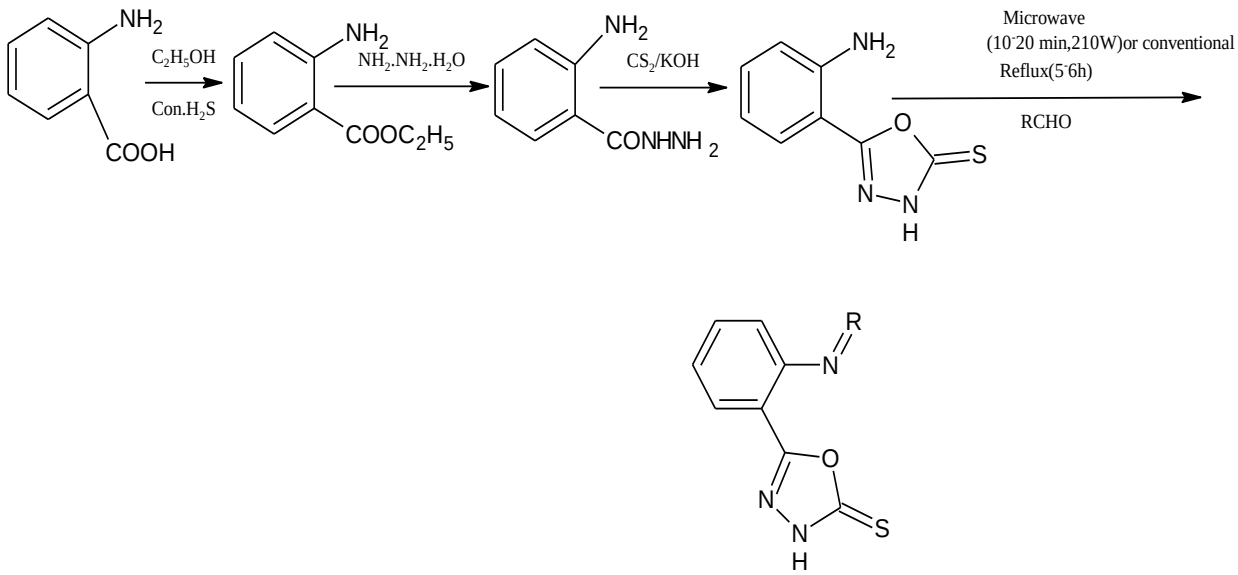
R: I, II, III, IV

**Scheme 4**

**Table 1**

| Acid Hydrazide (I) | 2-(4-chlorophenyl) amino-5-aryl-1,3,4-oxadiazole hydrochloride (III) | Yield (%) | MP(°C) | 2-(4-chlorophenyl) amino-5-4-aryl- 1,3,4-oxadiazole (IV) (free base | MP(°C) |
|---|---|---|---|---|---|
| 4-nitro benzohydrazide (Ia) | -5(4-nitrophenyl)-1,3,4-oxadiazole hydrochloride (IIIa) | 89 | 134 | -5(4-nitrophenyl)-1,3,4-oxadiazole (IVa) | 184 |
| Isonicotinic acid hydrazide (Ib) | -5(4-pyridinyl)-1,3,4- oxadiazole hydrochloride (IIIb) | 82 | 162 | -5(4-pyridinyl)-1,3,4-oxadiazole (IVb) | 174 |
| Phenyl acetic acid hydrazide (Ic) | -5-benzyl-1,3,4-oxadiazole hydrochloride(IIIc) | 78 | 154 | -5-benzyl-1,3,4-oxadiazole (IVc) 163 | 163 |
| Benzohydrazide (Id) | -5-phenyl-1,3,4-oxadiazole hydrochloride(IIId) | 74 | 118 | -5-phenyl-1,3,4-oxadiazole (IVc) 163 | 132 |
| 2-hydroxy benzohydrazide (Ie) | -5(2-hydroxyphenyl)-1,3,4-oxadiazole hydrochloride(IIIe) | 80 | 166 | -5(2-hydroxyphenyl)-1,3,4-oxadiazole (IVe) | 178 |
| 2-chlorobenzo hydrazide (If) | -5(2-chlorophenyl)-1,3,4-oxadiazole hydrochloride(IIIf) | 70 | 126 | -5(2-chlorophenyl)-1,3,4-oxadiazole (IVf) | 151 |

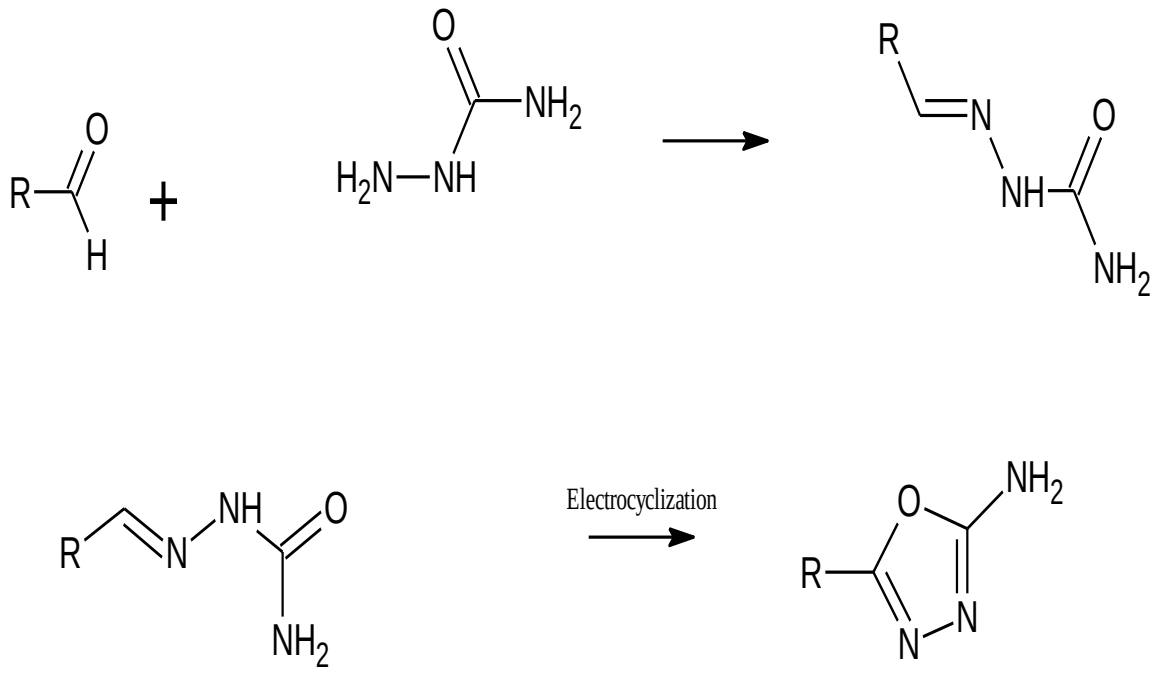
A: p-$NO_2C_6H_4$; B: -$C_5H_4N$; C-$CH_2C_6H_5$; D: - $C_6H_5$; E: -O-$OHC_6H_4$; F-O-$ClC_6H_4$




**Scheme 5**

**Table 2**

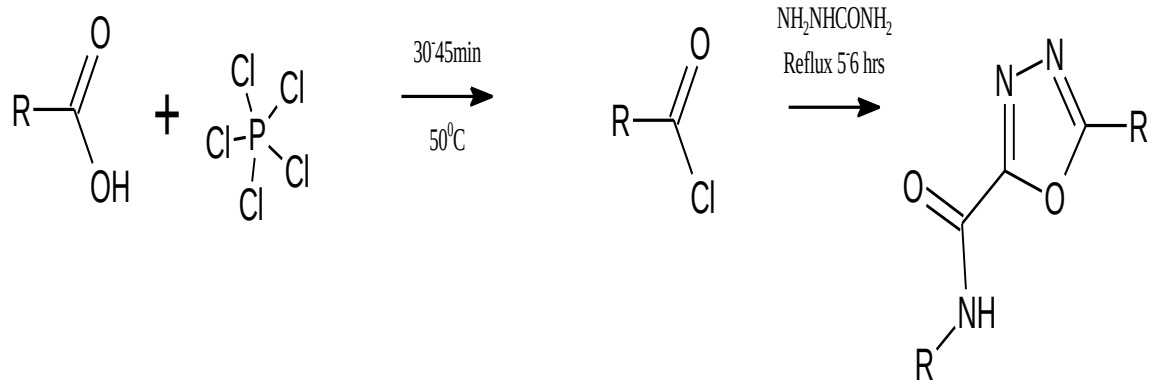
| Compound | R | Conventional Synthesis | | Microwave Synthesis | | MP(°C) |
|---|---|---|---|---|---|---|
| | | Time (hrs) | Yield % | Time(min) | Yield % | |
| A | 2-Br | 5 | 62 | 10 | 75 | 180-182 |
| B | 3-Br | 5 | 68 | 12 | 77 | 110-112 |
| C | 4-Br | 6 | 66 | 11 | 73 | 185-187 |
| D | 4-$OCH_3$ | 5 | 59 | 12 | 64 | 160-162 |
| E | 4-F | 5 | 75 | 12 | 88 | 185-187 |
| F | 2-Cl | 6 | 65 | 14 | 78 | 168-170 |
| G | 3-Cl | 5 | 69 | 13 | 89 | 176-178 |
| H | 4-Cl | 5 | 64 | 15 | 86 | 170-172 |
| I | 4-OH | 6 | 73 | 10 | 82 | 137-139 |
| J | 2-$NO_2$ | 5 | 76 | 14 | 67 | 108-111 |




**Scheme 6**

**Table 3**

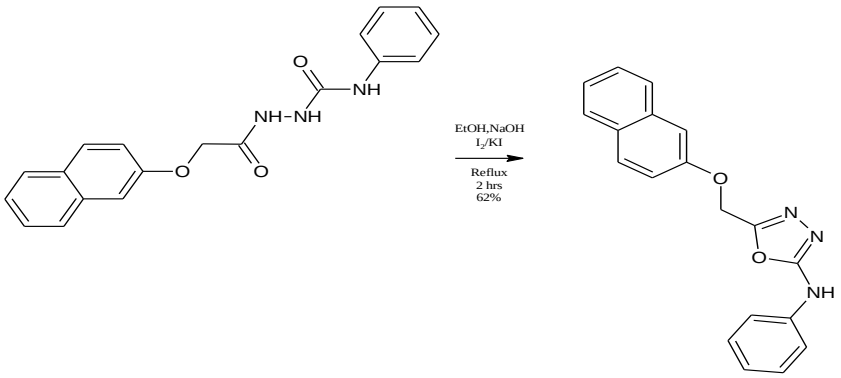
| R | Time (hr) | Applied Potential (V) | Current(A) | Yield in AcOH | Yield in $CH_3CN$ | Time (hr) Conv. | Yield Conv. |
|---|---|---|---|---|---|---|---|
| o-$BrC_6H_4$ | 4 | 1.54 | 0.11 | 88 | 80 | 6 | 76 |
| m-$BrC_6H_4$ | 5 | 2.10 | 0.15 | 96 | 92 | 6 | 71 |
| p-$BrC_6H_4$ | 5 | 2.25 | 0.12 | 86 | 81 | 6 | 68 |
| o-($NO_2C_6H_4$) | 3 | 1.85 | 0.09 | 92 | 90 | 5 | 86 |
| 3-pyridinyl | 4 | 1.80 | 0.07 | 79 | 75 | 9 | 75 |
| $CH_2Cl$ | 5 | 2.00 | 0.12 | 75 | 73 | 5 | 78 |
| $CHCl_2$ | 5 | 1.90 | 0.08 | 81 | 77 | 4 | 77 |
| p-($CH_3C_6H_4$) | 3 | 1.95 | 0.09 | 85 | 81 | 7 | 69 |
| 3,4,5-trimethoxy benzoyl | 5 | 1.70 | 0.08 | 92 | 84 | 9 | 63 |
| 1-$C_{10}H_7$ | 4 | 1.60 | 0.10 | 87 | 81 | 9 | 69 |
| 2-$C_{10}H_7$ | 4 | 2.20 | 0.12 | 86 | 78 | 8 | 72 |



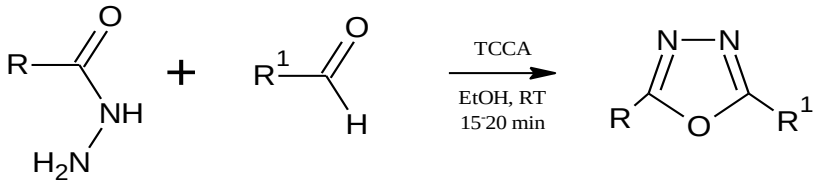

**Scheme 7**

**Table 4:** The physical properties of the synthesized compounds are given below:[51]

| Compound | R | Mol. Formula | Yield (%) | MP (°C) |
|---|---|---|---|---|
| $C_1$ | $-C_6H_5$ | $C_{15}H_{11}N_3O_2$ | 72 | 212 |
| $C_2$ | o-$C_6H_5Cl$ | o-$C_{15}H_9N_3O_2Cl_2$ | 66 | 214 |
| $C_3$ | m-$C_6H_5Cl$ | m-$C_{15}H_9N_3O_2Cl_2$ | 79 | 213 |
| $C_4$ | p-$C_6H_5Cl$ | p-$C_{15}H_9N_3O_2Cl_2$ | 82 | 211 |
| $C_5$ | o-$C_6H_5NO_2$ | o-$C_{15}H_9N_5O_6$ | 80 | 273 |
| $C_6$ | m-$C_6H_5$ $NO_2$ | m-$C_{15}H_9N_5O_6$ | 73 | 266 |
| $C_7$ | p-$C_6H_5$ $NO_2$ | p-$C_{15}H_9N_5O_6$ | 78 | 271 |



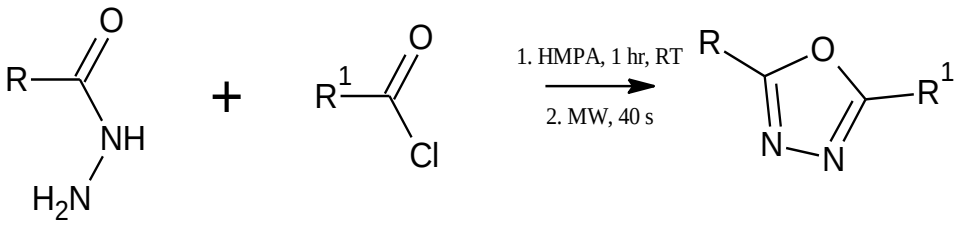

**Scheme 8**




R: -Ph, 4-$ClC_6H_4$, 4-$OCH_3C_6H_4$, 4-$CH_3C_6H_4$

$R^1$: -Ph, 4-$ClC_6H_4$, 4-$OCH_3C_6H_4$, 4-$CH_3C_6H_4$

**Scheme 9**




R: -Ph, 4- $NO_2Ph$, 4-MeOPh, 4-pyridyl

$R^1$: 2-propyl, 2-thienyl, 4-$NO_2Ph$, 4-MeOPh

**Scheme 10**

**Scheme 3**

**Synthesis of glycine containing di-1,3,4-oxadiazole ring (1–7)**

- Preparation of methoxymethyl benzoate (compound 1): The compound was prepared as per the procedure described by Brian.[38] Yield (95%); mp: 49–51 °C.
- Preparation of methoxybenzoyl hydrazine (compound 2): The compound was prepared as per

the procedure described by Smith (1946).[39] Yield (91%); mp: 135–137 °C.

- Preparation of (4-methoxyphenyl)-1,3,4-oxadiazole-2-thione (compound 3): To the resulting compound 2 (1.66 g, 0.01 mol) in ethanol (20 mL), potassium hydroxide (0.56 g, 0.01 mol) in water (5 mL) and carbon disulfide (2 mL, 0.03 mol) were mixed and refluxed (5 h). The reaction mixture was then cooled and diluted with cold water (30 mL) followed by acidification with 10% hydrochloric acid. The percentage yield of the product was reported to be 84% and melting point: 199–201 °C.
- Preparation of (4-methoxyphenyl)-1,3,4-oxadiazole-2-ethoxycarbonylsulfanyl (compound 4): Compound 3 (2.08 g, 0.01 mol) in an excess of ethyl chloroformate (3 mL) was heated under reflux for 5 h. Yield (79%); melting point: 124–125 °C.
- Preparation of 5-(4-methoxyphenyl)-1,3,4-oxadiazole-2-hydrazine-carbonylsulfanyl (compound 5): The compound was also prepared by the same method as described above for compound 2. Yield (87%); mp: 222–224 °C.
- Preparation of 4-(4-methoxybenzenesulfonyl)-hippuric acid (compound 6): Glycine (1.5 g, 0.02 mol) in 1 N sodium hydroxide solution (20 mL) was cooled at 0–5 °C and the cold solution was added in dropwise manner to 4-methoxybenzoyl chloride (3.41 g, 0.02 mol) in chloroform (30 mL). The mixture was then subjected to continuous stirring. The aqueous layer was separated, acidified and filtered. Colorless needles were obtained. Yield (83%); mp: 178-180°C.
- Preparation of N-{5-[5-(4-methoxyphenyl)-1,3,4-oxadiazole-2-yl- sulfanyl]-1,3,4-oxadiazole-2-yl-methyl}-4-methoxybenzamide (compound 7) : Compound 5 (2.66 g, 0.01 mol) and Compound 6 (2.09 g, 0.01 mol) were refluxed with phosphorous oxychloride (5 mL) for 24 h and then carefully treated with ice water and made basic by the addition of concentrated sodium bicarbonate solution. The filtered product was dried and recrystallized using ethanol–DMSO (10/1) solvent. Yield (69%); mp: 193–195 °C.[40]

**Scheme 4**

**Synthesis of 2-(4-chlorophenyl) amino-5-(4-nitrophenyl)-1,3,4-oxadiazole (1) & 2-(4-chlorophenyl) amino-5-aryl-1,3,4- oxadiazole (2)**

The 4-nitro benzohydrazide (Ia) was boiled with N-(4-chlorophenyl) isocyanodichloride (II) in chloroform for 3 hrs. The hydrogen chloride gas evolved was carefully observed. The sticky mass formed was distilled off.

The solid was obtained after frequent washings with petroleum ether. The separated solid turned blue litmus red. It was then recrystallized from ethanol, m.p: 134°C. This upon treatment with dilute ammonium hydroxide solution liberated free bases (2). The liberated substance was recrystallized from aqueous ethanol (70%), m.p: 184 °C and was found to be water insoluble. However the product dissolved in organic solvents.

The above reaction was also extended to other acid hydrazides (Ia-f) and relatively higher yields of the products were isolated.[41]

**Scheme 5**

**Synthesis of Some Schiff bases of 1,3,4-oxadiazole**

Certain Schiff bases of 1,3,4-oxadiazole were prepared by using an aromatic amine [5-(2-aminophenyl)-1,3,4-oxadiazole-2(3H)-thione] and a carbonyl compound (substituted benzaldehyde) by nucleophilic addition reaction.

Step 1: General Synthesis

To a solution of anthranilic acid (0.05mole, 6.85g) in ethanol, conc. sulphuric acid was added dropwise and shaked for few min till a white coloured precipitate of ethyl-2-aminobenzoate was formed. To this, hydrazine hydrate (0.1mole, 4.85ml) was added and refluxed. Potassium hydroxide (3g) and carbon disulphide (10ml) were added to the resultant mixture and again refluxed. TLC was monitored to assess the reaction completion. The resultant solution was cooled and added to ice cold water and acidified with dil. HCl (10%) to about pH 5. The solid product formed was collected and dried.

Step 2: Synthesis of schiff base of 1,3,4-oxadiazole derivatives (compounds a-j)

***Conventional Method***

To a solution of the above compound (0.01 mole, 1.93g) in ethanol (5ml), substituted benzaldehyde and glacial acetic acid (GAA) were added and refluxed (5-6 h). TLC was monitored to check the reaction completion. The solid mass formed was separated. Pure product was obtained after recrystallization.

***Microwave Irradiation Method***

To a solution of the above compound (0.01 mole, 1.93g) in ethanol (5ml), substituted benzaldehyde and few drops glacial acetic acid were added and irradiated (210 W) for 10-15 minutes. The solid product was obtained after cooling.[44]

**Scheme 6**

**Electro organic synthesis of 2-amino 5-substituted 1,3,4-oxadiazoles**

The synthesis was done by the electrochemical cyclization of semicarbazone 1, aldehyde 2 and semicarbazide 3.

The reaction mixture was prepared by dissolving adequate amount of substrate and supporting electrolyte in acetic acid. A solution of semicarbazone 3 (1.0g) was dissolved in acetic acid (100 mL). $LiClO_4$ (0.106 g) was

dissolved in the above keeping the strength of the supporting electrolyte at 0.01M. Semicarbazide hydrochloride (1.0 g) and NaOAc (1.0g) 2 were dissolved in water (10 mL) followed by the addition of aldehyde 1 (0.5 g) with continuous stirring. The mixture was then kept overnight.

The electrolysis was performed at room temperature in a 250 mL three cell electrode assembly with platinum plate (flattened sheet of dimension 1.0 cm x 0.5 cm) as counter electrode and saturated calomel electrode (SCE) as reference electrode.[45] The reaction mixture was stirred using magnetic stirrer.

The current-potential data was recorded at an interval of 15 min using a potential cum galvanostat. (Table 1).[46-49] Acetonitrile can also used in place of acetic acid and extraction of products were done in a similar manner. The electrolysis was completed in 3-5 hrs. The solid products formed were coloured and completely different from that of the starting materials.

The products were isolated by extraction with solvent. Distilled water was used for the initial dilution of the reaction mixture. The two immiscible layers got separated which were then transferred to a separating funnel and shaken for a few min. The organic layer containing the product was filtered off and left overnight. Coloured crystals of the oxadiazoles 4 were isolated after the evaporation of solvent.[50]

Reagents: Aromatic acid hydrazide (I)[42] & 4-chlorophenyl isocyanodichloride(II)[43]

**Scheme 7**

**Synthesis of compounds $C_1$ to $C_7$**

The reagents phosphorus pentachloride and benzene were taken in an RB flask in 1:1 molar ratio. The flask was then fitted with air condenser and calcium chloride guard tube. It was heated at around 50°C with vigorous shaking. The excess $POCl_3$ was distilled out after 30 min. The residue was taken and dried well. Then, semicarbazide was added to the respective acid chloride and refluxed for 5 h. Simultaneous monitoring of TLC was done to check the reaction completion. The excess benzene was distilled off. Then the solid was then made neutral with aq. $NaHCO_3$ followed by extraction with chloroform. The crude product was obtained through the distillation of chloroform under reduced pressure.

**Scheme 8**

**Synthesis of 1,3,4-oxadiazol-2-amines from the cyclization reaction of acylthiosemicarbazides with iodine**

Cyclization reaction of acylthiosemicarbazides using iodine as oxidizing agent yielded 5-substituted-2-amino-1,3,4-oxadiazoles. El-Sayed and co-workers[52] reported the synthesis of 5-((naphthalen-2-yloxy)methyl)-N-phenyl-1,3,4-oxadiazol-2- amine by heating compound a in ethanol in the presence of sodium hydroxide and iodine in potassium iodide. The yield was found to be 62%.

**Scheme 9**

**Synthesis of 1,3,4-oxadiazoles using trichloroisocyanuric acid (TCCA)**

Pore and co-workers[53] developed an efficient method for the one-pot synthesis of unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles from trichloroisocyanuric acid (TCCA) at optimum temperatures. The mild nature of the reaction and short time duration were the main advantages. The yield was found to be 75-85%.

**Scheme 10**

**Microwave synthesis of 2, 5-disubstituted-1,3,4-oxadiazoles**

A variety of 1,3,4-oxadiazole derivatives have been prepared by the microwave condensation of monoarylhydrazides with acid chlorides using HMPA as the solvent. This method was rapid, produced excellent yields and required no catalytic support. About 45-95% of the product was obtained.[54]

## CONCLUSION

This review, has outlisted certain synthetic protocols for the derivatives of 1,3,4 oxadiazole reported in the former publications. Furthermore, the different synthetic schemes figured above may serve as a tool in designing novel compounds having the 1,3,4-oxadiazole unit. Many of the synthesized molecules are also being analysed and screened for their respective biological activities. The various citations hold strong evidence on the broad spectrum activity profile of this class of compounds. Research works are still being done on the 1,3,4-oxadiazole moiety for the exploration of its pharmacological potential which could become a landmark in the medical history.

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