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A Review on Synthesis of Various Oxadiazole Derivatives Applying Green Chemistry Methods

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ABSTRACT

Green chemistry is the chemistry of new world, it is also called as sustainable chemistry and green chemistry prevents the use and generation of hazardous substances. Microwave irradiation, use of green catalysts, grinding or milling technique, electrochemical methods, and ultra sound mediated methods are some of the important green chemistry techniques. In the current review we discuss about green synthetic methods used for oxadiazole derivative synthesis. Oxadiazoles are important class of heterocyclic compound with wide therapeutic uses and the techniques discussed here are helpful for the synthesis of more therapeutically relevant novel derivatives of oxadiazoles using more environmentally benign methods.

Keywords: Green chemistry, Microwave, Oxadiazole, Synthesis.

INTRODUCTION

Green chemistry can be defined as design of chemical products and process in such a way that it reduce or eliminate the use or generation of hazardous substances, not only at the final stage of synthesis or process but throughout the life cycle of chemical product,

The green approach must begin from the design of experiment to the ultimate disposal of waste after the synthesis [1].

Green synthetic approach gives importance not only to the elimination of hazardous waste but it concentrates on safety, energy efficacy, environment, human health and all other factors to make the process a greener one.

Green chemistry focuses on earth's sustainable resources also. The green chemistry approach begun in US in the year 1990 based on pollution prevention act. The approach is based on 12 basic principles which reduce or eliminate the impact of dangerous chemicals as well as chemical processes on our environment and life [2].

PRINCIPLES OF GREEN CHEMISTRY

Prevention

This principle explains about the prevention of waste and bi-products, it is better to prevent the formation of wastes than treating the formed hazardous waste in to non-hazardous one.

E-factor is used as a measure of waste production, it was describes by Roger Sheldon, which relates the weight of waste co-produced to the weight of the desired product.

E-Factor=Total waste (kg)/Total product (kg)

Higher the E-factor more waste production, and therefore the environmental impact is also more. It is advisable to have a process with low E-factor [3].

Maximize atom economy

Chemical synthetic processes should be designed to maximize incorporation of all substances used in the process into final product.

Atom economy, Atom selectivity or atom utilization helps to prevent the pollution at molecular level. The atom economy can be achieved by using basic chemical building blocks as starting materials rather than breaking down complex molecules and rejecting most of it as waste.

% of atomic efficiency=(relative molecular weight of the desired product/relative molecular weight of all reactants) × 100 [4].

Design less hazardous chemical synthesis

The third principle advocates the use of methods and chemicals which are less hazardous to environment and living beings, the green approach encourage replacing toxic chemicals with biological enzymes, modified catalysts, less corrosive solvents which are safe to use [5].

Design safer chemicals and products

Designing safer chemicals with efficiency is a challenge for chemists, certain chemicals may bind to metabolic enzymes other electron-poor molecules are carcinogenic. Fat soluble chemicals may deposit in body. Therefore it is very important to design chemical products that are fully effective yet have little or no toxicity [1].

Use safer solvents and reaction conditions

Fifth principle encourages the use of safer solvents and other reaction conditions (separation agents, recrystallizing solvents)

The principle says avoid use of solvents and other auxiliaries; if it is inevitable use safer chemicals. Replace petrochemical solvents with non-hazardous solvents, like water supercritical fluids; gas expanded liquids, ionic liquids, liquid polymers and solvents derived from biomass [6].

Design for energy efficiency

Reactions must run at room temperature and pressure whenever possible for maximum energy efficiency, the energy requirement for a particular reaction must [2].

Use renewable feed stocks

Seventh principle of green chemistry encourages the use of renewable feedstock or starting material rather than depletable. Depletion of petroleum feed stocks is a rising concern and its energy consumption is also more therefore the principle suggests the use of renewable feed stocks of biological/agricultural origin as well as renewable energy sources like solar energy, wind power, hydropower, biomass energy and bio fuels.

Avoid chemical derivatives

While synthesizing the target molecule unnecessary derivation must be avoided, derivation requires more and different reagents like blocking or protecting groups, and which results in more waste.

Use of smart catalysts

Promote the use of catalysts, not stoichiometric reagents. Replace chemical catalysts with biodegradable catalysts, they are energy efficient, catalysts remain unchanged during the course of reaction and can be re-used, stoichiometric reagents are used in excess and carry out a reaction only once. Green catalysts are recoverable and are prepared from readily available materials and must comply with the rules and principles of green chemistry [7].

Degradable design

To reduce waste accumulation in the environment design chemical products in such a way that they break down into innocuous degradation products [8].

Prevent pollution by real-time analysis

Chemical process and products must be monitored thoroughly to prevent the formation of dangerous substances, new methods and techniques must be developed to ease the real time analysis of chemical process and products [9].

Minimize accidents and hazards

Process, starting materials must be safer, that is chemicals and process must be safer and chance of occurring of any accidents and hazards must be prevented [10].

OXADIAZOLE

As the name indicates oxadiazole is a member of organic compounds known as Azoles, azoles are five membered heterocyclic compounds containing one or more nitrogen in the ring, with or without other hetero atoms in ring [11].

Oxadiazole is a five membered heterocyclic ring; the five members making the rings are two carbons, two nitrogen and one oxygen atom. Oxadiazoles are dominant parts in molecules having physiological activity. Oxadiazoles are used as bioisosteric groups in place of amide, ester functional groups [12] (Figure 1).

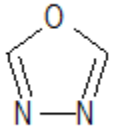

Figure 1: An oxadiazole moiety.

Discovery of oxadiazoles was done in the year 1884 by Tiemann and Krüger. There are four isomeric forms of oxadiazole exist (Figures 2-5).

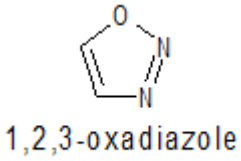

Figure 2: 1, 2, 3-Oxadiazole.

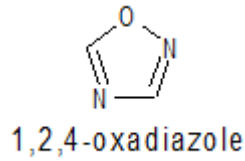

Figure 3: 1, 2, 4-Oxadiazole.

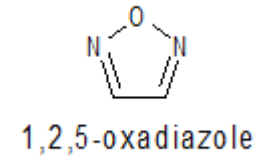

Figure 4:1, 2, 5-Oxadiazole.

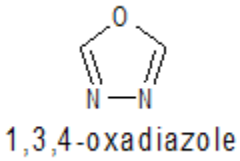

Figure 5: 1, 3, 4-Oxadiazole.

From the literatures it's found that 1,2,3 –Oxadiazole and 1,2,5 oxadiazoles and their derivatives show less significant medicinal activity in comparison with 1,2,4 oxadiazole and 1,3,4 oxadiazole [13].

1,2,4-and 1,3,4-Oxadiazoles are present in many drugs and biologically active compounds, the 1,2,4-oxadiazoles are substituted at C3 and C5 positions, 1,3,4-Oxadiazoles are substituted at position number C2 and C5 positions.

These derivatives show variety of biological activity like antiviral, anticancer, anti-tubercular, anxiolytic, anti-inflammatory and many more.

Below are some examples for drugs which are derivatives of oxadiazole (Figures 6-13).

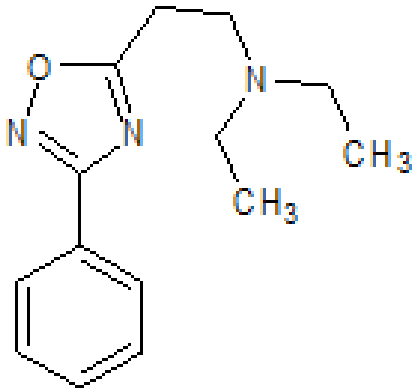

Figure 6: Oxolamine.

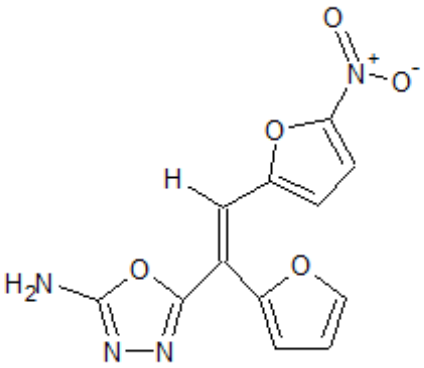

Figure 7: Furamizole.

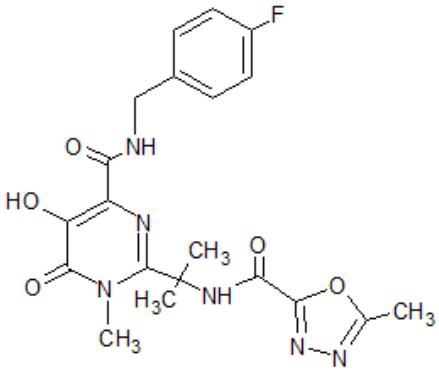

Figure 8: Raltegravir.

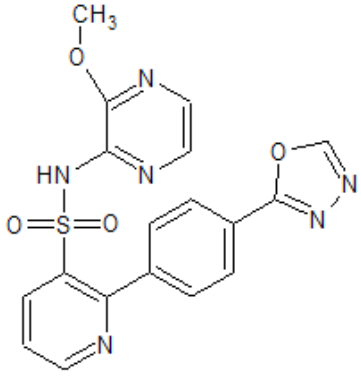

Figure 9: Zibotentan.

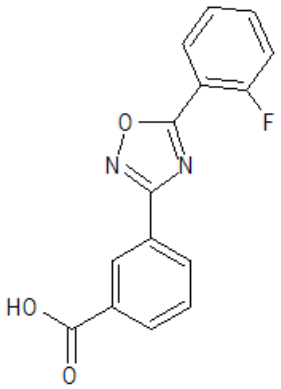

Figure 10: Ataluren.

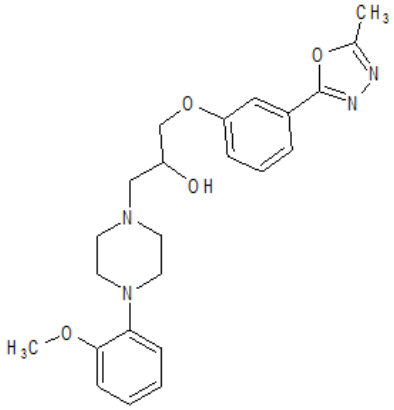

Figure 11: Nesapidil.

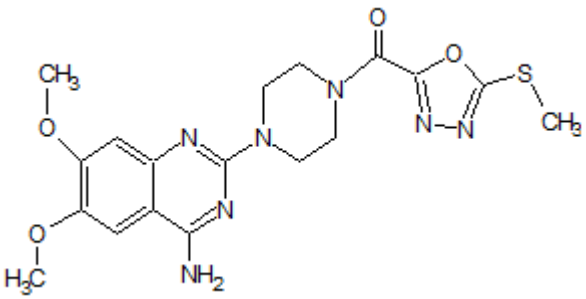

Figure 12: Tiodazosin.

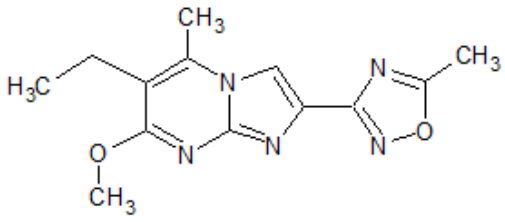

Figure 13: Fasipolen.

Examples of drugs molecules containing oxadiazole heterocycle

Oxolamine is a phenyl oxadiazole derivative which is used as cough suppressant, its IUPAC name is diethyl [2-(3-phenyl-1, 2, 4-oxadiazol-5-yl) ethyl] amine. Furamizole is a nitro derivative of 1, 3, 4-oxadiazole, its IUPAC name can be written as 2-Amino-5-(2-(5-nitro-2-furyl)-1-(2-furyl)-vinyl)-1, 3, 4-oxadiazole.Furamizole is a strong antibacterial agent [14, 15].

Raltegravir is an anti-viral drug, used for HIV infection, this is an HIV integrase inhibitor, which inhibits HIV integrase HIV integrase which is required of the replication of the virus [16]. IPAC name of raltegravir can be written as N-[(4-fluorophenyl)methyl]-5-hydroxy-1-methyl-2-{2-[(5-methyl-1,3,4-oxadiazol-2-yl)formamido]propan-2-yl}-6-oxo-1,6-dihydropyrimidine-4-carboxamide.Zibotentan is a new anti-cancer drug containing 1,3,4-oxadiazol in the structure, this is an endothelin receptor antagonist (ERA).It is investigated for its use in prostate cancer [17]. Ataluren is a novel drug developed to treat Duchenne muscular dystrophy (DMD), which is due to nonsense mutation of gene [18]. IUPAC name of Nesapidil is 1-[4-(2-methoxyphenyl) piperazin-1-yl]-3-[3-(5-methyl-1, 3, 4-oxadiazol-2-yl) phenyl] propan-2-ol, it is a drug used in anti-arrhythmic therapy [19]. Tiodazosin is an alpha 1 adrenergic antagonists used as an antihypertensive agent, it is a 1, 3, 4-oxadiazol derivative, IUPAC name can be written as [4-(4-amino-6, 7-dimethoxyquinazolin-2-yl) piperazin-1-yl]-(5-methylsulfanyl-1, 3, 4-oxadiazol-2-yl) methanone [20].

Fasiplon is a 1, 2, 4 oxidiazole derivatives it is a non-benzodiazepine anxiolytic drug [21].

In current review we are making an attempt to review various Green synthetic methods of biologically active oxadiazole derivatives. Green synthetic procedure we reviewed in the current article include microwave assisted method, grinding method, green catalysts assisted methods, electro-chemical method and ultra sound assisted method. Green synthetic methods are important because it addresses the challenges we face in synthetic chemistry, it reduces the waste or by-products produced during synthetic pathways, the methods in Green synthesis are environmental friendly and it reduces or monitor the use non-renewable feed stokes, it maximize the desired product and minimize toxic by-products and wastes [22].

GREEN SYNTHETIC APPROACHES FOR OXADIAZOLE SYNTHESIS

Micro wave assisted method of oxadiazole synthesis

Micro wave assisted synthesis one of the main methods of greener synthesis is energy efficient, much less waste and by products are produced in micro wave assisted methods.

Micro wave assisted synthetic methods are simple yet energy efficient and fast. Microwave irradiation is used in thermally driven organic transformation. In conventional heating method reactant molecules are slowly activated and take more time to complete the reaction and the method is not an energy efficient one. But microwaves couples directly on reacting molecules and it results in rapid rise in temperature and the process does not depends on the thermal conductivity of the reaction vessel as a result instantaneous localized super heating occur and the reaction takes place in faster rate [23].

Sahoo et al. synthesized a series of Schiff base containing 1, 3, 4 oxadiazole derivative using micro wave irradiation as well as conventional method.

In the first method 5-(2-aminophenyl)-1,3,4 oxadiazole-2-thione was synthesized in general method, from anthranilic acid, anthranilic acid was treated with ethanol, in presence of conc. Sulfuric acid, precipitate of ethyl-2 amino benzoate was obtained. Hydrazine hydrate was added in to the formed ester mixture and refluxed for 6 h, potassium hydroxide and carbon disulphide were added in to it and refluxed until hydrogen sulfide evolution stopped. Mixture is cooled and acidified with HCl, the formed solid 5-(2-aminophenyl)-1, 3, 4 oxadiazole-2-thione is re crystallized.

In green synthetic method 5-(2-aminophenyl)-1,3,4 oxadiazole-2-thione is dissolved in ethanol and made a solution, to it few drops of glacial acetic acid (GAA) was added and irradiated with micro wave radiation at power level 210 W for 10-15 minutes getting 1,3,4 oxadiazole derivatives.

When compared with the conventional method green synthesis is faster and less corrosive chemicals are involved in green synthesis [24] (Figure 14).

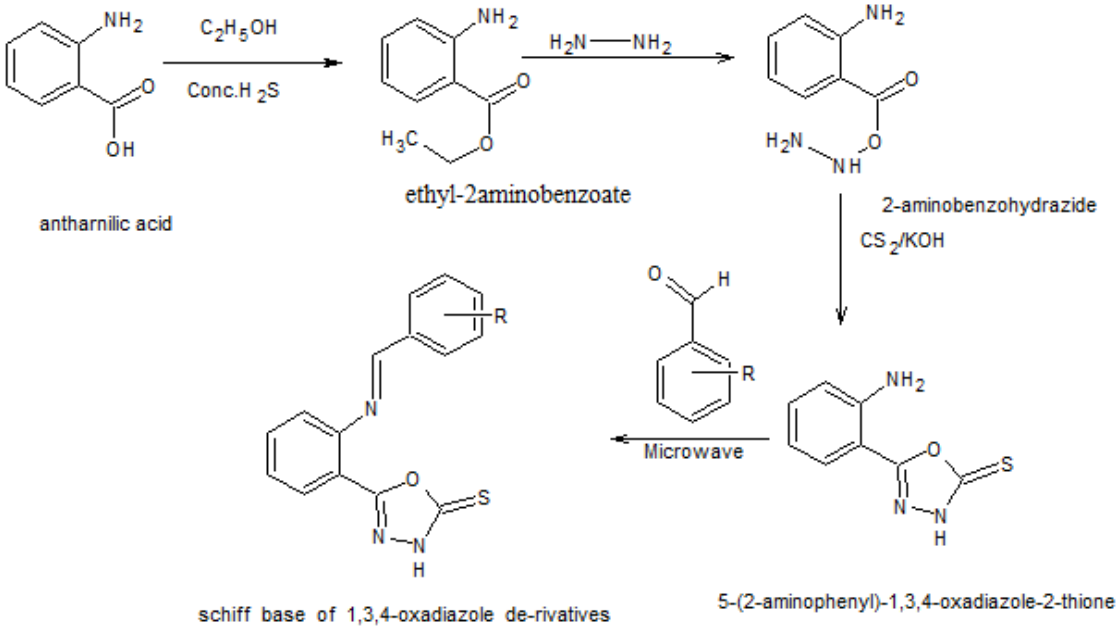

Figure 14: Micro wave assisted method of oxadiazole synthesis.

Adib et al. reported an efficient one pot synthesis of 3, 5-disubstituted 1, 2, 4-oxadiazoles under solvent-free conditions, the one pot synthesis was carried out in solvent free condition with the help of microwave irradiation. Different aryl nitriles react with hydroxyl amine in presence of acetic acid with microwaves irradiation to get amidoximes, the formed amidoximes undergo condensation reaction with the help of micro wave irradiation without solvents to produce high yield of 1,2,4-Oxadiazoles [25].

Khan et al. synthesized 2,5-Disubstituted-1, 3 ,4-Oxadiazoles using conventional method as well as microwave assisted method, they reported the micro wave assisted green synthesis was more efficient and, and the time consumed to complete the reaction was few minutes when compared with conventional method which took hours or even days, In the method various commercially available hydrazides where treated with different carboxylic acids in presence of phosphorous oxychloride to obtain 2,5-disubstituted 1, 3, 4-oxadiazoles [26] (Figure 15).

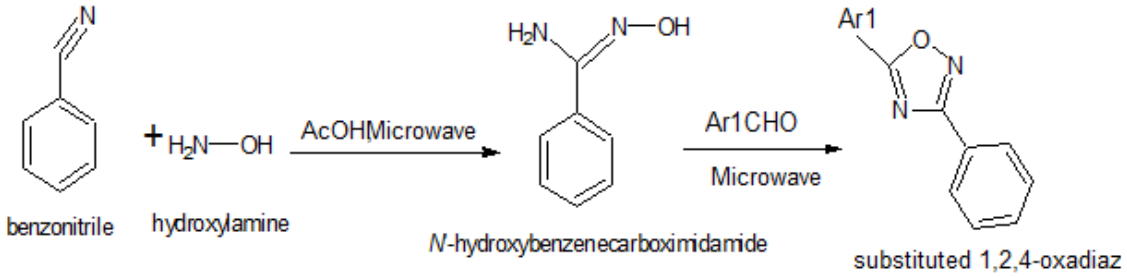

Figure 15: Substituted 1, 2, 4-Oxadiazole.

Gorjizadeh et al. reported One-Step Synthesis of 2,5-Disubstituted 1,3,4-Oxadiazoles by cyclization oxidation reaction of acyl hydrazides, in the synthesis they have selected solvent free condition, where acylhydrazide react with different aldehydes in presence of 1,4-bis (tri phenyl phosphonium)-2 butene peroxodisulfate (BTPPDS)under micro wave irradiation for 25 minutes [27] (Figure 16).

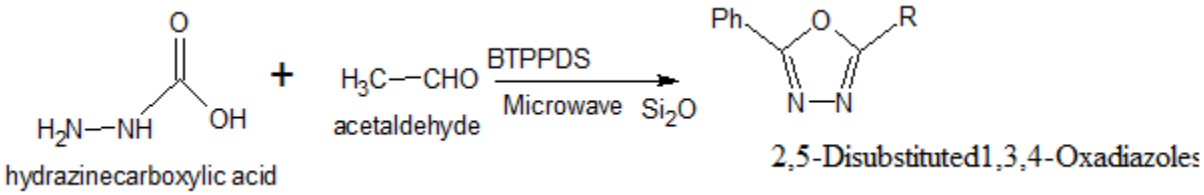

Figure 16: 2, 5-Disubstituted 1, 3, 4-oxadiazoles.

Baiju et al. reported micro wave assisted synthesis of novel isoniazid based oxadiazole derivatives, isoniazid react with various aromatic aldehydes in presence of microwave irradiation, the formed hydrazide react with chloramine T in ethanol in presence of microwave irradiation [28] (Figure 17).

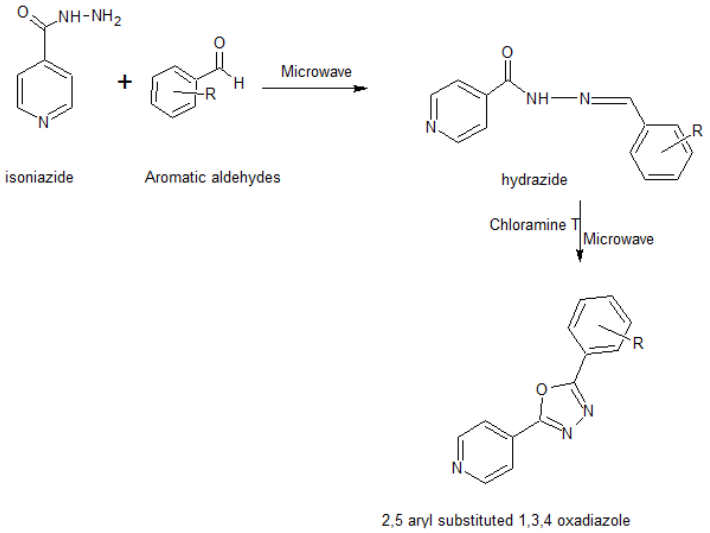

Figure 17: Synthesis of 2, 5 Aryl substituted 1, 3, and 4 oxadiazole.

Babak Kaboudin and Fariba Saadati synthesized 1,2,4-oxadiazoles from nitriles by a one pot green synthetic method from nitriles with hydroxylamine hydrochloride with the help of micro wave irradiation in presence of magnesia-supported sodium carbonate in a reaction with acyl halides under solvent-free conditions [29] (Figure 18).

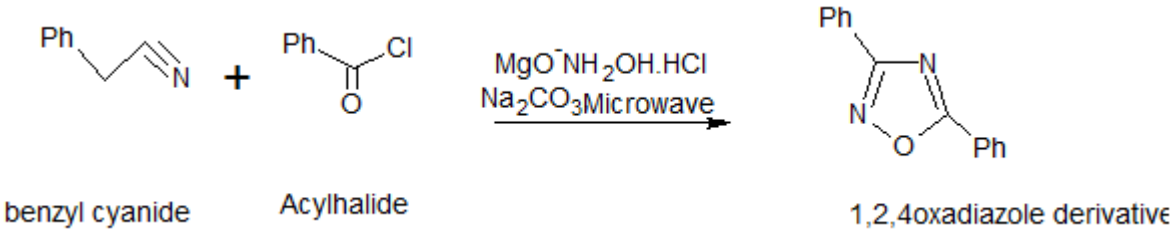

Figure 18: 1, 2, 4 Oxadiazole derivative.

Jaiprakash N. Sangshetti reported one pot synthesis of novel 2, 5-disubstituted 1, 3, 4-oxadiazoles using microwave irradiation, the synthesis involve reaction between hydrazide, aromatic aldehydes in ethanol using sodium bisulfite as catalyst. The synthesis was done in 15 minutes using micro wave irradiation, while in conventional method it took almost 10 hours [30] (Figure 19).

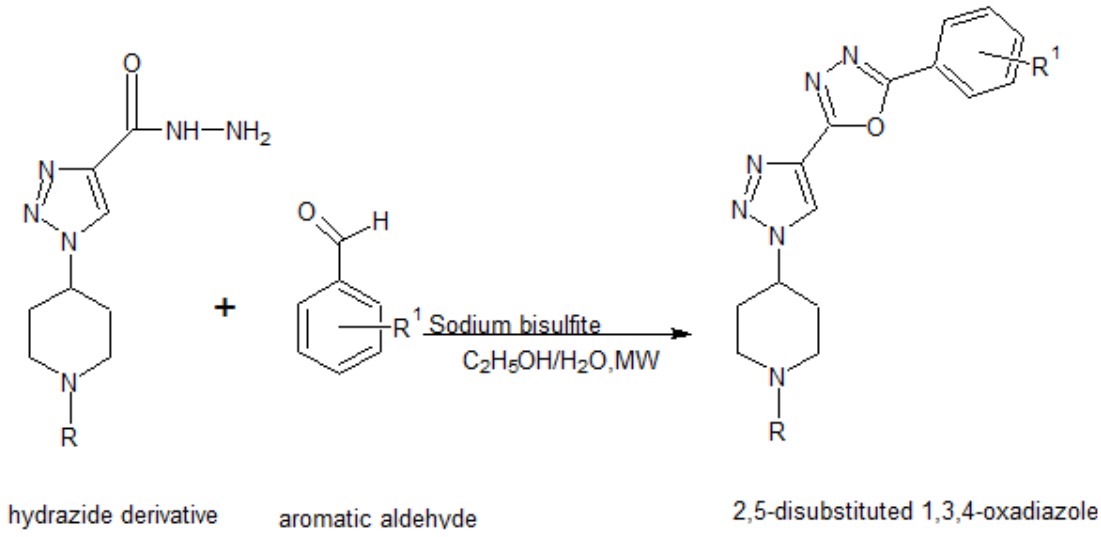

Figure 19: 2, 5-Disubstituted 1, 3, 4-oxadiazole.

Sauer et al. reported an ecofriendly method for the synthesis of 1,2,4-Oxadiazoles with the help of microwave irradiation from α-amino acids and amidoximes in acetone and water mixture as solvent, different solvents were screened, the best yield was observed in acetone/water mixture using Dicyclohexylcarbodiimide (DCC) as coupling agent, *in situ* synthesis of Chiral N-Protected Amino Acids and Aryl amidoximes was done and they are mixed thoroughly, the mixture was subjected to microwave irradiation at 100 W power, temperature of 1150 C, for 15 min to get the 1,2,4-Oxadiazole derivatives [31] (Figure 20).

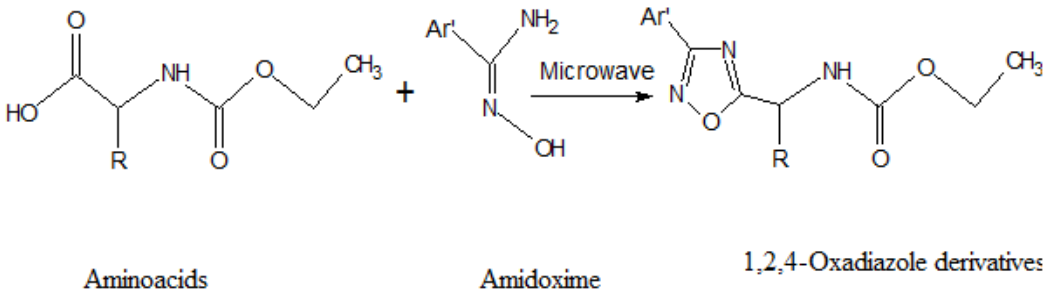

Figure 20: 1, 2, 4-Oxadiazoles.

Kaboudin and Saadati reported Novel Method for the Synthesis of 1, 2, 4-Oxadiazoles using Alumina Supported Ammonium Fluoride under Solvent-free Condition.

In the method amidoxime (benzamidoxime) react with acyl chloride (benzoyl chloride) giving 3, 5 diphenyl-1, 2, 4-oxadiazole in good yield, in presence of alumina supported ammonium fluoride with the help of micro wave irradiation. Ammonium fluoride acts as strong base in the reaction which helps in cyclization [32] **(**Figure 21).

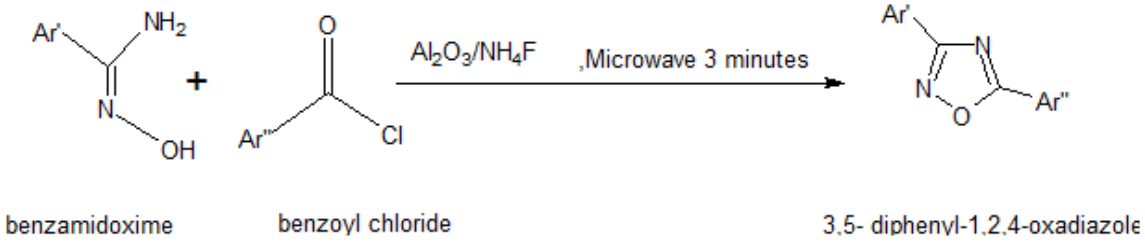

Figure 21: 3, 5 Diphenyl-1, 2, 4-oxadiazole.

Sujit et al. reported a micro wave assisted method for synthesis of biphenyl-2-oxadiazoles,the first step of method involves reaction between 4'-methyl-[1,1'-biphenyl]-2-carboxilic acid and Hydrazine hydrate in microwave irradiation at d 250 °C, with 250 psi maximum pressure, the process get completed within 7 minutes giving 4'-methyl-[1,1'-biphenyl]-2-carbohydrazide.

In the second step the formed hydrazide along with substituted aromatic acids and phosphorus oxychloride was made to paste by grinding thoroughly, the homogeneous mixture was then heated by irradiating micro wave radiation at 160 W. The reaction took 5 to 6 minutes to get complete [33] **(**Figure 22).

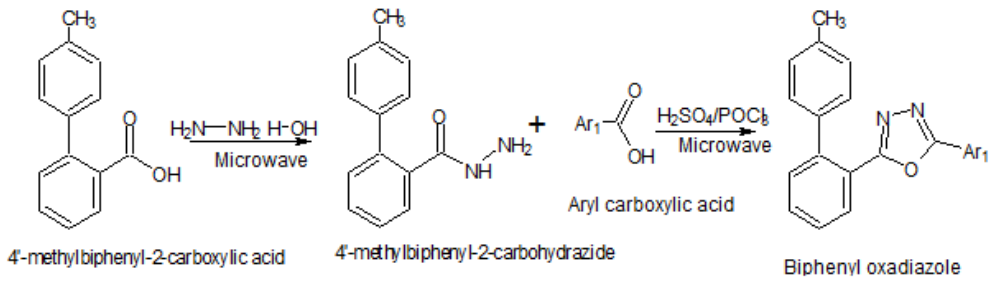

Figure 22: Biphenyl oxadiazoles.

Frank et al. reported nitro imidazole containing oxadiazole derivative synthesis with the help of microwave irradiation in solvent free environment. In the scheme 2-methyl-4-nitro-imidazole, is used synthesis imidazole-hydrazide. A mixture of formed imidazole hydrazide with suitable carboxylic acids in the presence of phosphorous oxychloride was irradiated with microwave radiation to get 5-aryl-2-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazoles [34] **(**Figure 23).

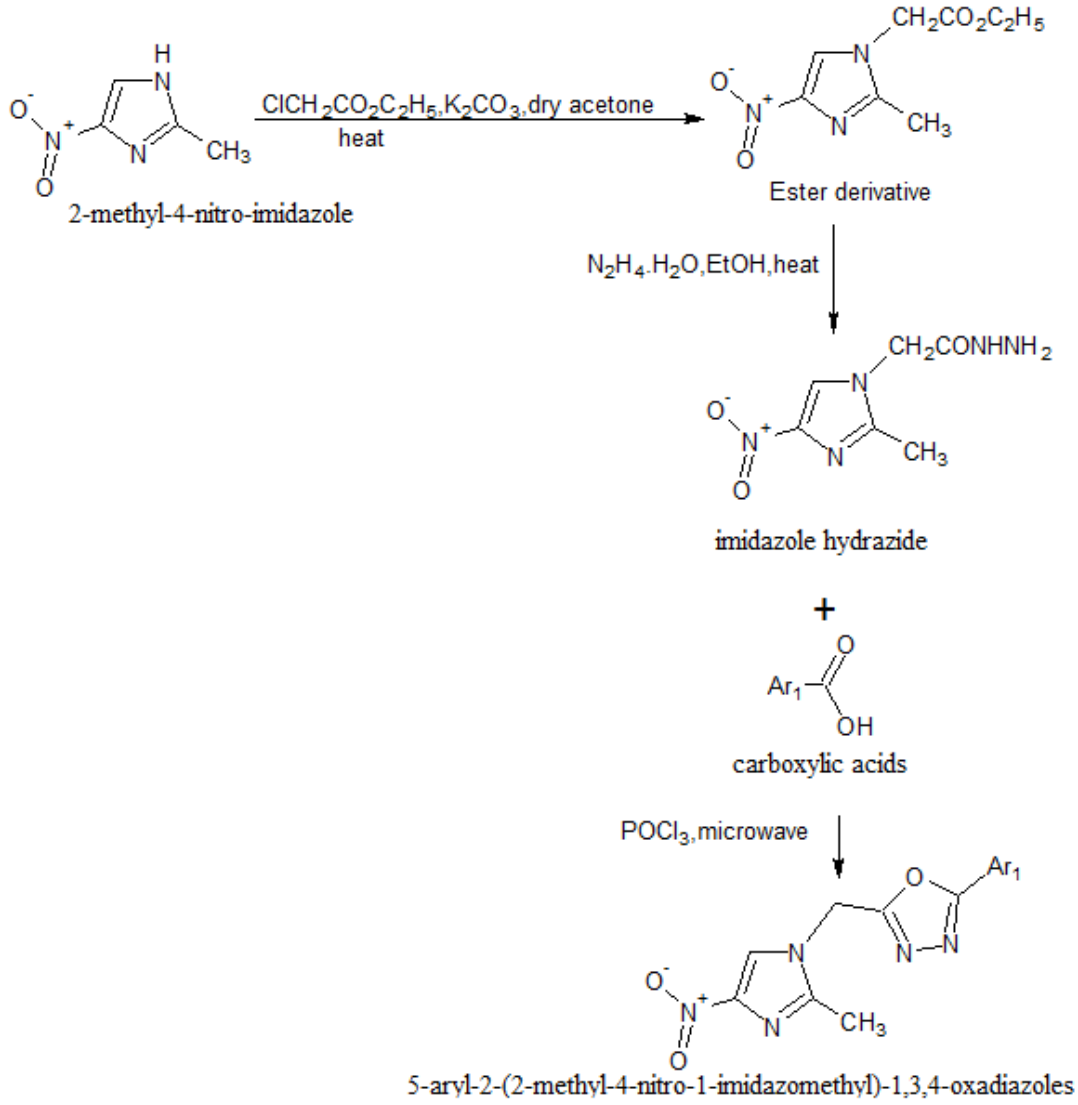

Figure 23: 5-Aryl-2-(2-methyl-4-nitro-1-imidazomethyl)-1, 3, 4-oxadiazoles.

Yadav et al. synthesised 1,3,4 oxadiazole having promising anticancer activity, novel anticancer oxadiazole derivatives are synthesised by microwave assisted green synthetic method. The starting material methyl di-nitro benzoate was synthesized *in situ* by the influence of microwave from 3, 5 dinitro benzoic acid and methanol using sulphuric acid as catalyst, and the ester formed was refluxed for 5 minutes with hydrazine hydrate in microwave irradiation to get 3, 5 dinitro benzohydrazide, which was next refluxed with cyanogen bromide in methanol in presence of microwave irradiation getting 5-(3, 5-dinitrophenyl)-1, 3, 4-oxadiazole-2-amine.

The above formed 1, 3, 4-oxadiazole derivative in acetone reacted with aroyl isothiocyanates to afford carbamothioyl derivatives of 1, 3, 4 oxadiazole with promising anticancer activity [35] **(**Figure 24).

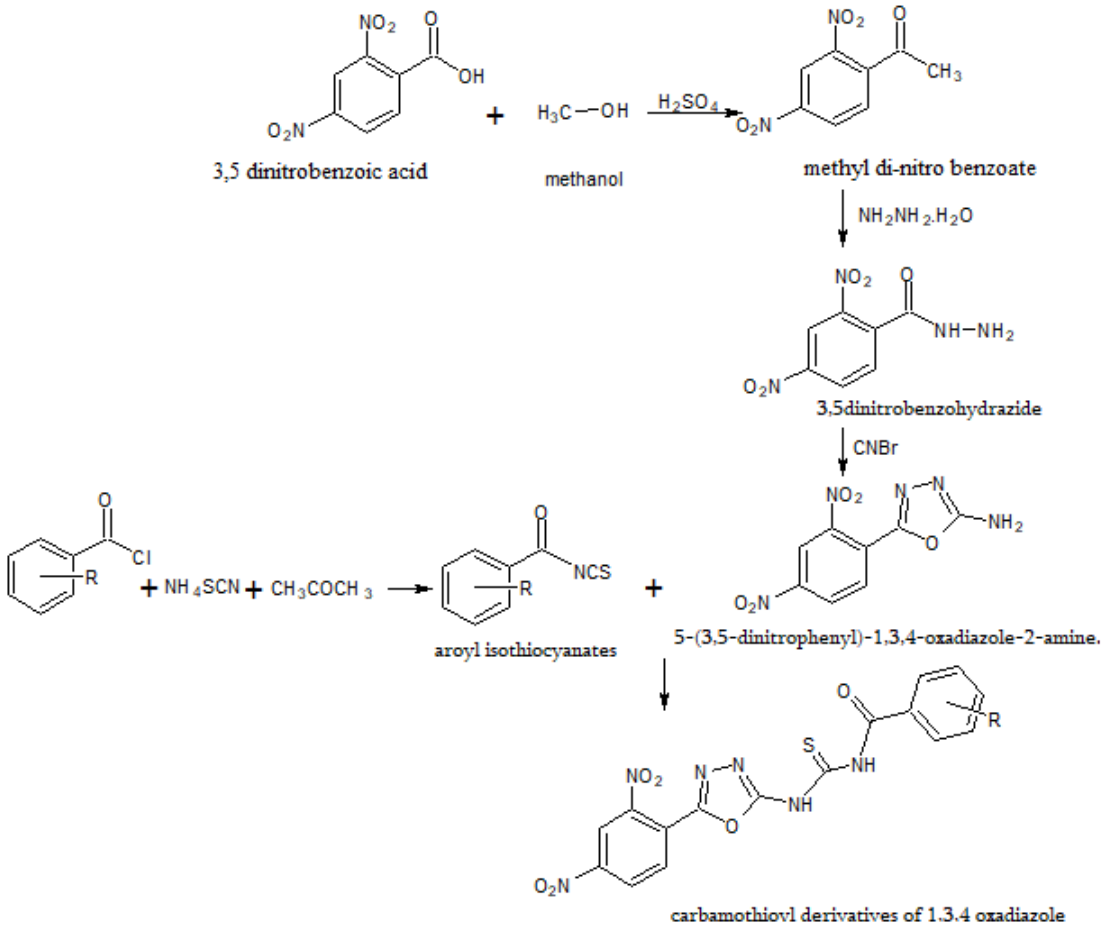

Figure 24: Carbamothioyl derivatives of 1, 3, and 4 oxadiazole.

Green catalysts for oxadiazole synthesis

Catalysts are used in a reaction to reduce the activation energy and thus facilitate the reaction. In green chemistry to make the reactions more environmental friendly, effective green chemistry use catalysts which are more environmentally benign. The method avoids the use of corrosive catalysts and chemicals. The heterogeneous catalysts used in green synthesis can be recovered and recycled [36].

Visible light assisted green synthesis is catalyzed in presence of photo redox catalysts was reported by Cai, a novel green synthetic approach for the synthesis of 2,5-Dihydro-1,2,4-oxadiazoles.The method is a [3+2] cyclo addition reaction of azirines with nitrosoarens with the assistance of visible light using organic dye photo redox as catalyst [37] **(**Figure 25).

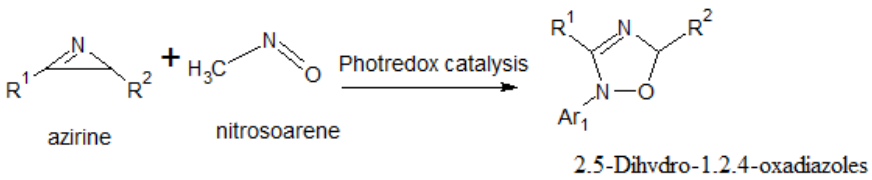

Figure 25: 2, 5-Dihydro-1, 2, 4-oxadiazoles.

Yadav and Yadav reported visible light induced oxidative cyclization of aldehydes and acyl hydrazides to yield 2,5-disubstituted-1,3,4-oxadiazoles.The reaction proceeds in aerobic environment in the presence of eosin Y as an organophotoredox catalyst[38] (Figure 26).

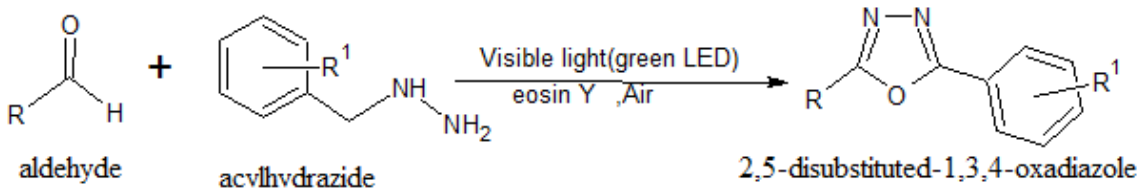

Figure 26: 2, 5-Disubstituted-1, 3, 4-oxadiazoles.

Ayhan Y reported an eco-friendly novel method for the synthesis of 1,3,4-Oxadiazole-2(3H)-thiones, the method involves *in situ* cyclization of hydrazine carbodithioate potassium salts under normal phase micelle media catalysis promoted by an anionic surfactant sodium dodecyl sulfate (SDS), solvents involved as water as well as ethanol. The method gave high yield of products and it took only 2 hours for the completion of reaction where the conventional methods take 24 hours [39] (Figure 27).

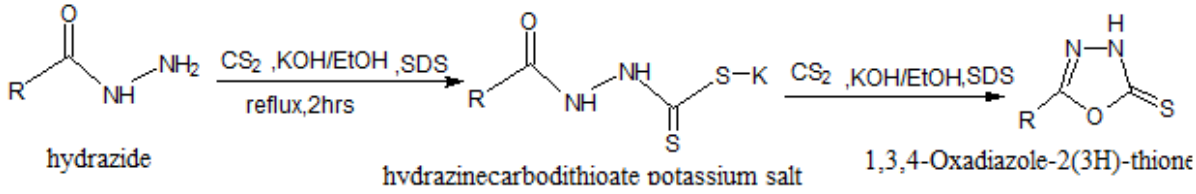

Figure 27: 1, 3, 4-Oxadiazole-2(3H)-thiones.

Bakht et al. synthesized 1,3,4-oxadiazole derivatives by a double greener synthesis, where they used green catalyst and the reaction was carried out in water, the catalyst used was Cesium salt of tungsto phosphoric acid, the catalyst is effective, safe and strongly acidic in nature, moreover it is water tolerant, Tungsto phosphoric acid salt is prepared by using cesium carbonate and aqueous solution of tungsto phosphoric acid, 2-amino-5-chloro-anthranilic acid hydrazide and different aldehydes are stirred in presence of prepared Cesium tungsto phosphoric (CsPW) acid catalyst in deionized water, the oxadiazole derivatives are separated from the organic layer by extracting the reaction mixture using diethyl ether, catalyst was recovered from the aqueous layer [40] (Figure 28).

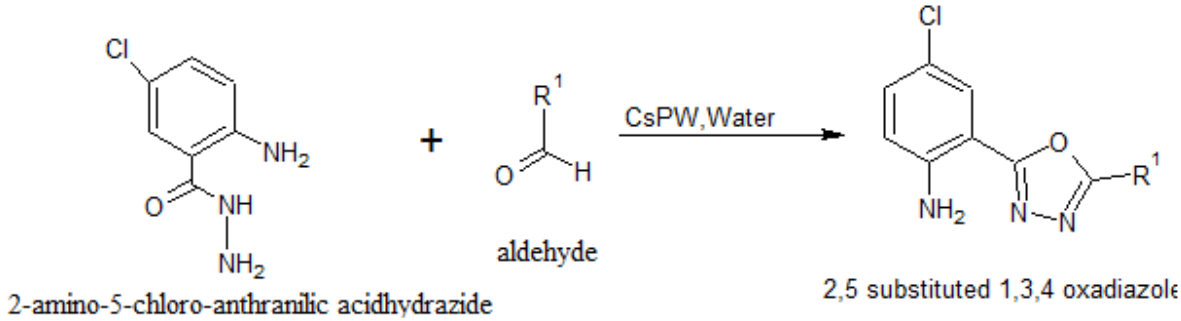

Figure 28: 1, 3, 4-Oxadiazole.

Mohamed S. Behalo*, Ebtsam S. El said reported Green synthesis of 1,3,4-oxadiazole derivatives based on N-arylidene 2-(1-oxo-4-(4-phenoxyphenyl)phthalazin-2(1H)-yl)acetohydrazide,hydrazide was prepared, by treating 2-(4-phenoxybenzoyl)benzoic acid with hydroxyl amine in pyridine, giving 4-(3-phenoxyphenyl)-1H-benzo[d][1,2]-oxazin-1-one,this on reaction with ethyl glycinate in ethanol in the presence of sodium acetate to give ester. The formed ester reacted with hydrazine hydrate to yield (1-oxo-4-(4-phenoxyphenyl)phthalazin-2(1H)-yl) aceto hydrazide, the hydrazide was used as starting material for the synthesis of oxadiazole derivatives, cerium (IV) ammonium nitrate (CAN)as a catalyst, hydrazide react with various aldehydes to get corresponding hydrazones, the formed hydrazones are ground with CAN catalyst under solvent free condition in room temperature gives 2, 5-diaryl-1,3,4 oxadiazole derivatives.

Conversion of hydrazones to oxadiazole derivatives was based on cyclization oxidation reaction of formed hydrazones.

A higher yield of oxadiazole derivatives was found in one pot reaction where the hydrazide was react with various aromatic aldehydes and CAN in in aqueous dichloromethane as a solvent [41] (Figure 29).

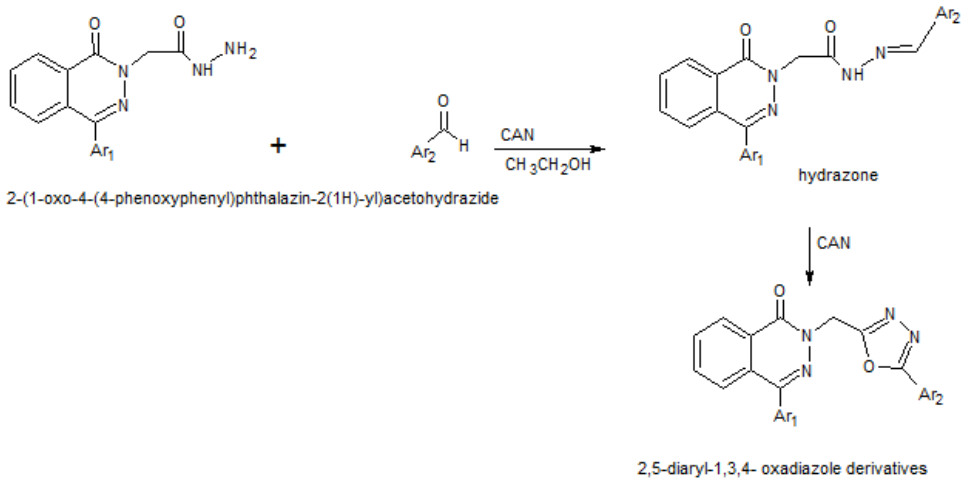

Figure 29: 2, 5-Diaryl-1, 3, 4 oxadiazole derivatives.

Polshettiwar and Varma reported a green synthetic one pot synthesis of 1, 3, 4-oxadiazoles using solid supported Nafion NR50 as catalyst under microwave irradiation without any solvent. In the reaction various hydrazides reacted with triethylorthoformate, triethylorthoproponate and triethylorthobenzoate to get desired 1, 3, 4-oxadiazoles in good yield [42] (Figure 30).

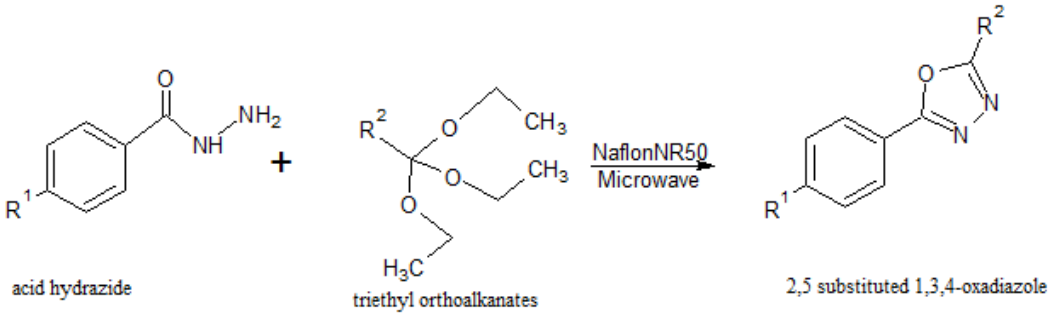

Figure 30: 1, 3, 4-Oxadiazoles.

A similar method was reported by Agnieszka Kudelko, Wojciech Zielinski in the method cinnamic acid hydrazide reacted with triethylortho esters and the reaction was carried out under micro wave irradiation for 10 minutes at 125◦ [43] (Figure 31).

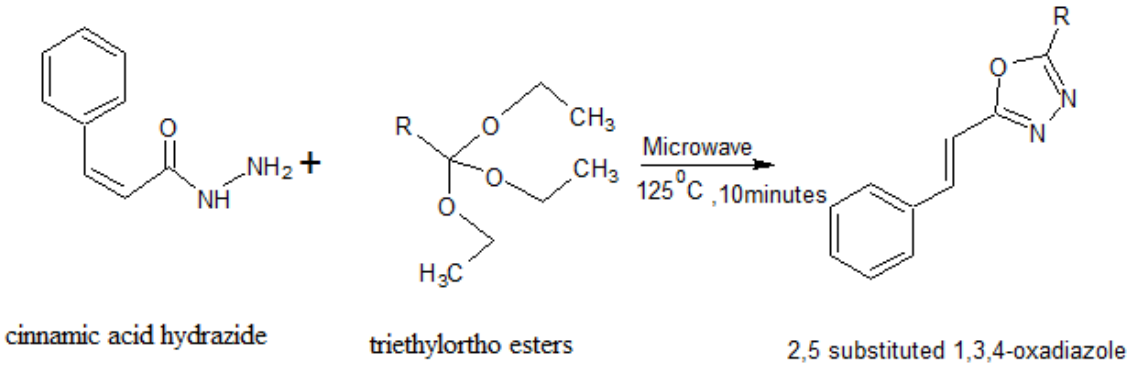

Figure 31: 2, 5 Substituted 1, 3, 4-oxadiazole.

Grinding an effective green synthetic method

Grinding or milling is a technique in Green chemistry technique; it is one of the mechano chemistry techniques. The method is rapid, clean and effective and it can be carried out in solvent free environment [44].

Toda et al. showed many exothermic reactions can be done with high yield by just grinding reagents using mortar and pestle. In grinding method reactions are initiated by transfer of very small amounts of energy through friction, the grinding method is not only energy efficient but produce very less waste. The reactions takes place with the help of grinding are simple, cheaper and easy to handle.

Chattopadhyay and Ray reported an effective method to convert semi carbazones to oxadiazole derivative by grinding, the principle mechanism is oxidative cyclization.

The reaction carried out in room temperature, aryl semi carbazone, potassium bromide, potassium bromate and oxalic acid dehydrate was mixed thoroughly for 20 minutes, mixture is treated with excess water to yield oxadiazole derivatives [45] (Figure 32).

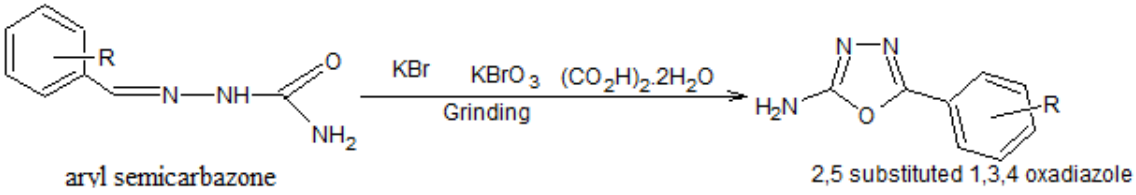

Figure 32: 2, 5 Substituted 1, 3, 4 oxadiazole.

Kumar and Makrandi synthesized unsymmetrical 2, 5-disubstituted 1, 3, 4-oxadiazoles, using grinding technique, the reaction was between aromatic hydrazides with aryl aldehydes, they are ground in the presence of molecular iodine in a mortar, and the reaction took place in a single step, the reaction is a better greener alternative for the synthesis of oxadaizole derivatives and the synthesis was carried out without organic solvents.

The scheme shows suitable aldehyde and aromatic hydrazine was ground with iodine to remove iodine from the formed product after confirming the completion of reaction by TLC, ice cold solution of sodium thiosulphate was added. This method use minimum number of organic reagents and organic solvents are completely omitted.

This is a very efficient and less time consuming method, grinding was done only for 5 to 10 minutes [46] (Figure 33).

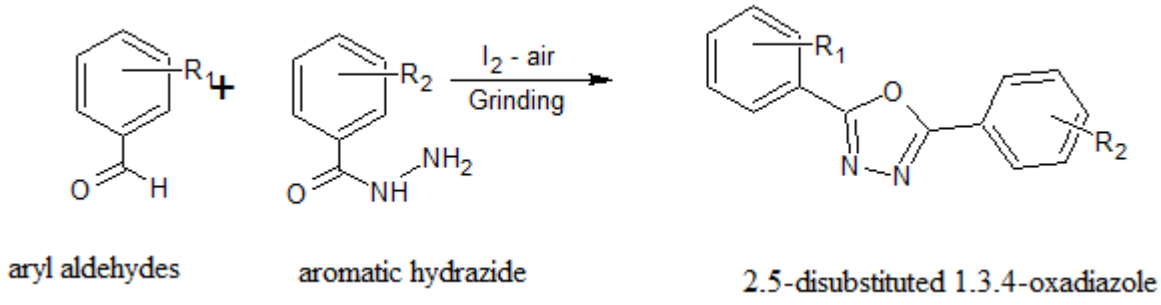

Figure 33: 2, 5-Disubstituted 1, 3, 4-oxadiazoles.

Taha et al. synthesized different 1,3,4 oxadiazole derivatives by grinding method in presence of Iodine as catalyst, the hydrazides used in the method are phenyl hydrazide and 4-hydroxy hydrazide, each hydrazide is mixed with different substituted benzaldehydes and catalytic amount of iodine was added and the mixture was ground for 8 minutes [47] (Figure 34).

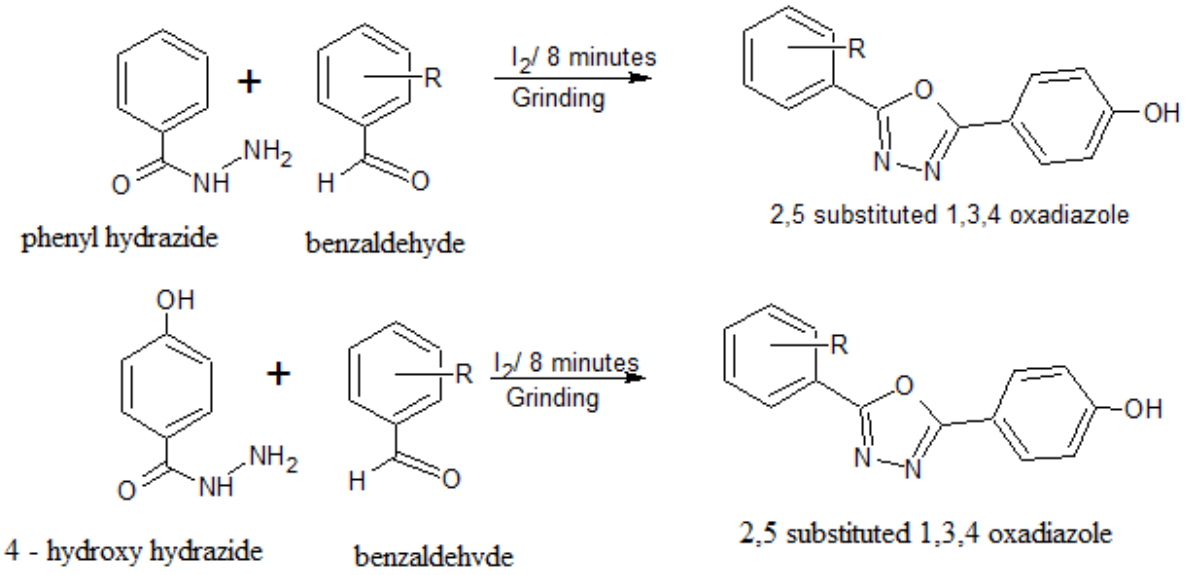

Figure 34: 2, 5-Disubstituted 1, 3, 4-oxadiazoles.

Sankaram et al. reported a highly effective green synthetic method for the synthesis of 1, 3, 4 oxadiazole (2-(2-(3-nitrophenyl)-1, 8-naphthyridin-3-yl)-5-aryl-1, 3, 4-oxadiazole). The method involve grinding of hydrazine hydrate, aryl aldehyde and oxidative cyclization with $FeCl_36H_2O$ in solvent-free solid-state condition to afford 2-(2-(3-nitrophenyl)-1, 8-naphthyridin-3-yl)-5-aryl-1, 3, 4-oxadiazole [48] (Figure 35).

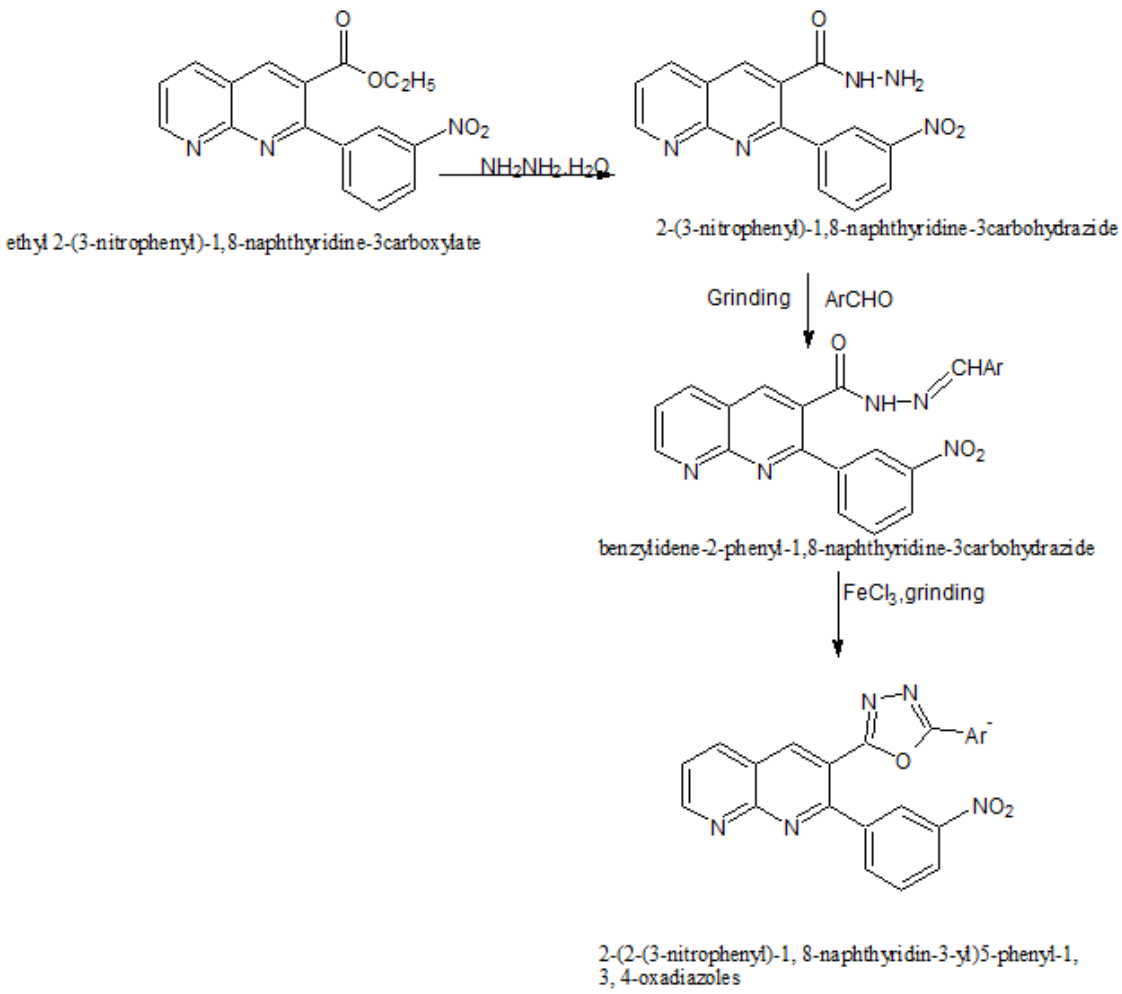

Figure 35: 2-(2-(3-Nitrophenyl)-1, 8-naphthyridin-3-yl)-5-aryl-1, 3, 4-oxadiazole.

Electro chemical method as a green synthetic approach

Sharma et al. reported green synthetic method of 2-amino-5-substituted 1, 3, 4-oxadiazoles, the scheme involves electro chemical technique that is anodic oxidation of semi-carbazone at platinum anode in acetic acid. Electrochemical cyclization green synthesis avoids hazardous waste chemicals produced in conventional method [49] (Figure 36).

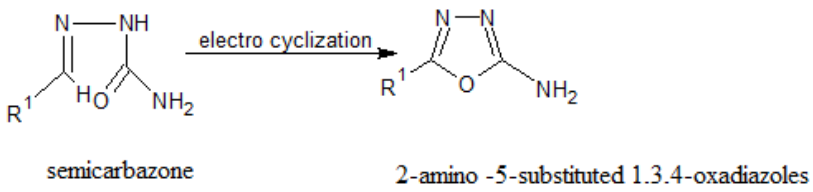

Figure 36: 2-Amino-5-substituted 1, 3, 4-oxadiazoles.

Gao and Wei reported an efficient oxidative cyclization of N –acyl hydrazones for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles, the reaction was carried out in presence of tert-butyl hypoiodite (t-BuOI) which is generated which is generated *in situ* from t-BuOCl and NaI. Reaction carried out in DMC [50] (Figure 37).

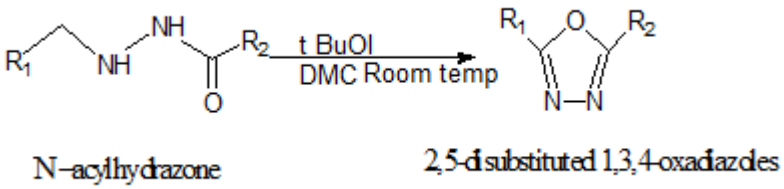

Figure 37: 2, 5-Disubstituted 1, 3, 4-oxadiazoles.

Singh et al. reported a green synthetic method for 2,5-disubstituted 1,3,4-oxadiazoles the method used is anodic cyclization, different N'-Benzylidene benzo hydrazides were selected and electrolysis of the selected hydrazides in the presence of a LiClO as supporting electrolyte in anhydrous MeCN was carried out at room temperature resulting in 2,5-diphenyl-1,3,4-oxadiazole,the starting materials were consumed completely no wastage of chemicals was found in the method [51] (Figure 38).

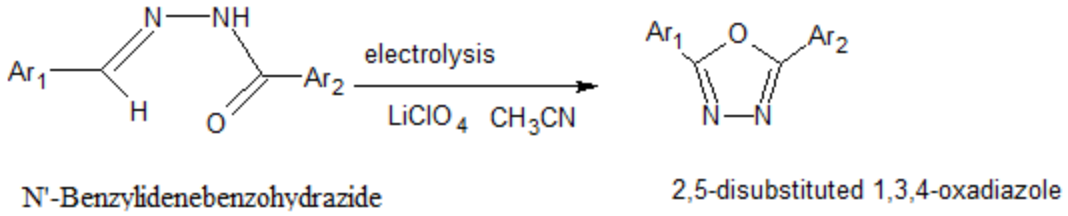

Figure 38: 2, 5-Disubstituted 1, 3, 4-oxadiazoles.

Kumar reported synthesis of novel 2-amino-5-substituted-1, 3, 4-oxadiazoles using anodic oxidation of semi carbazone, semi carbazone was prepared *in situ* in the reaction by the reaction between semi carbazide, aldehyde and sodium acetate, the formed semi carbazone undergone electrolysis in non-aqueous electrolyte acetic acid and lithium perchlorate was as a supporting electrolyte, platinum plate as working as well as counter electrode and saturated calomel electrode as reference electrode. Anodic oxidation takes place, the product was extracted from the electrolyte by solvent extraction technique [52] (Figure 39).

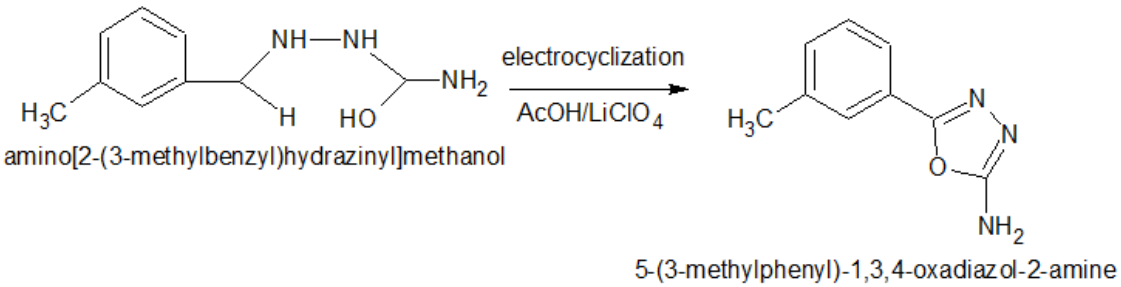

Figure 39: 5-(3-Methylphenyl)-1, 3, 4-oxadiazol-2-amine.

Similar synthesis of 2, 5-Disubstituted-1, 3, 4-Oxadiazoles was reported by Lotfi et al. where acetonitrile containing lithium perchlorate was used as electrolyte. Starting material 4-Methoxybenzaldehyde semi carbazone was synthesized by the reaction between 4 methoxy-benzaldehyde, semi carbazide hydrochloride and freshly recrystallized sodium acetate. The formed semi carbazone had undergone electrolysis in the above mentioned electrolyte using conventional electro chemical method. Precipitated product was separated from the electrolyte. [53] (Figure 40).

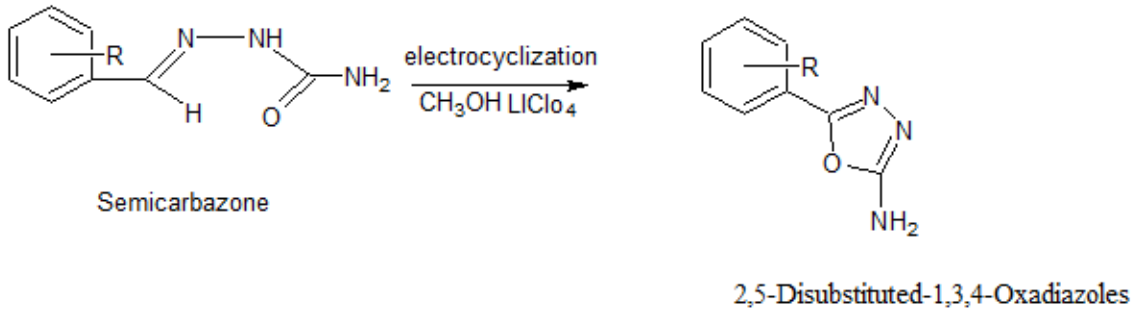

Figure 40: 2, 5-Disubstituted-1, 3, 4-Oxadiazoles.

Ultra sound mediated green synthesis

Ultra sound is used in green chemistry because it is an energy efficient activation technique; catalytic activity is also enhanced under ultrasound irradiation. Ultra sonic irradiation along with green solvents with or without catalysts improve the rate of the reaction [54]

Rouhani et al. reported synthesis of 2-aryl-1, 3, 4-oxadiazoles by using ultra sound waves, one of the important green synthetic methods, to the solution of *N*-iso cyanoiminotriphenylphosphorane in DCM added solution of different aryl benzoic acid derivatives was sonicated in an ultrasonic cleaner at room temperature, a 200 W of irradiation was sufficient to get good yield of oxadiazole derivatives [55] (Figure 41).

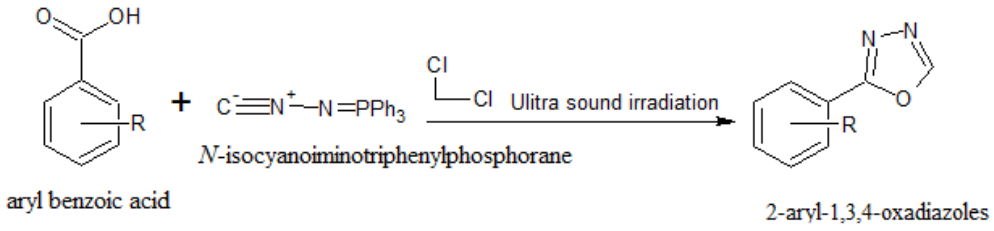

Figure 41: 2-Aryl-1, 3, 4-oxadiazoles.

Rouhani reported synthesis of fully substituted 1,3,4-oxadiazoles by green chemistry approach, with the help of ultra sound irradiation, the multi component reaction involve aromatic carboxylic acids, acenaphthoquinone, and (N-isocyanimino) triphenylphosphorane, the method used is accepted as a clean, efficient method for organic synthesis. Solvent used is acetonitrile [56] (Figure 42).

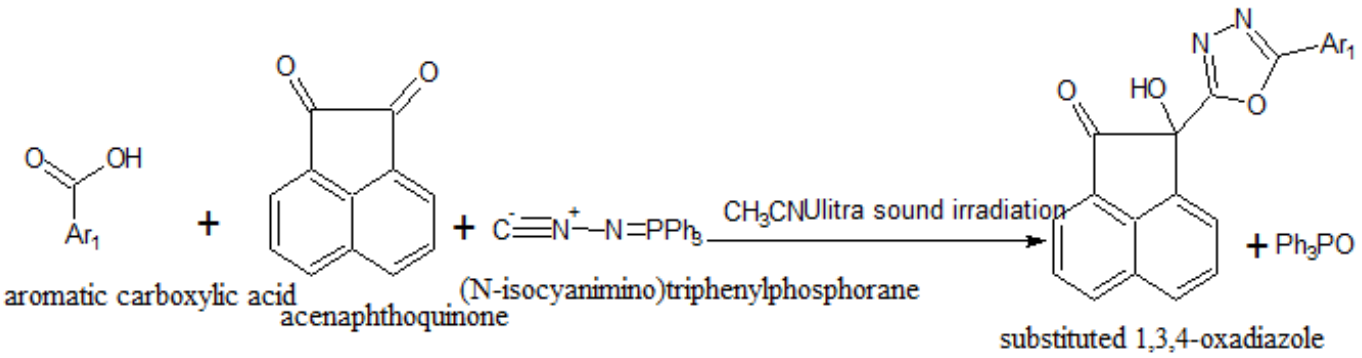

Figure 42: Substituted 1, 3, 4-oxadiazoles.

Yarmohammadi et al. reported a green synthetic approach for the synthesis of 5-substituted 1, 3, 4-oxadiazole-2-thiols in low solvent acid/base free synthesis. The method involves cyclo condensation of different aryl hydrazides with carbon disulfide with the help of ultra-sonic irradiation, in few drops of DMF [57] (Figure 43).

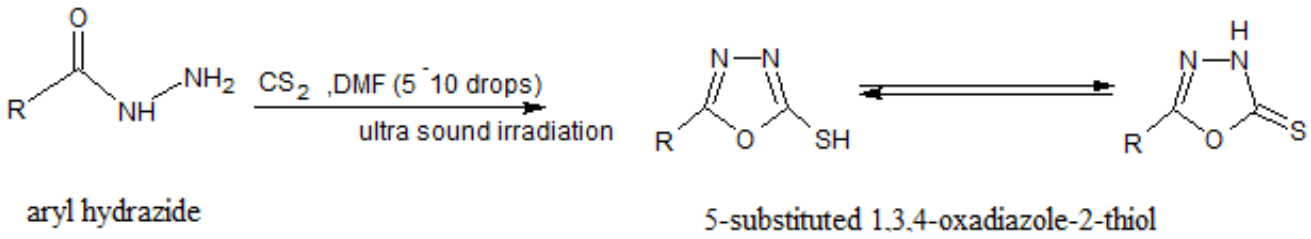

Figure 43: 5-Substituted 1, 3, 4-oxadiazole-2-thiols.

Ramzani et al. reported Ultra sound irradiation mediated method of synthesis of fully substituted 1,3,4-oxadiazole derivatives by a multi component one pot condensation reaction, the method involve use of N-isocyaniminotriphenylphosphorane, it is iso cyanide-based multi-component reaction (IMCR).The solvent chosen was dichloro methane as it gave a better yield compared to DMF, THF, CH_3CN, 1,4-dioxane, and EtOH, The reactants are biacetyl,4-metyl cinnamic acid N-isocyaniminotriphenylphosphorane in solvent dichloro methane, under the influence of ultra sound 100 W irradiation for 16 minutes gave better yield than that with 150 W irradiation for 16 min [58] (Figure 44).

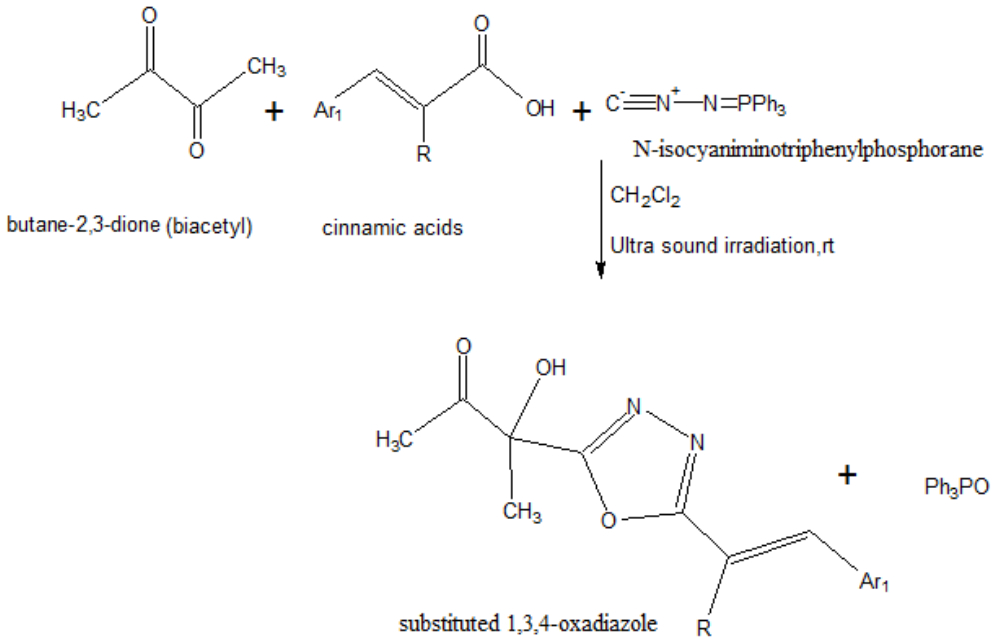

Figure 44: Substituted 1, 3, 4-oxadiazole derivatives.

CONCLUSION

Various green synthetic methods were discussed in the current review, and it is evident that all the methods discussed are more energy efficient, ecofriendly and high yielding when compared with conventional heating method of oxadiazole synthesis.

Since oxadiazoles are present in many biologically active molecules, their green synthetic methods are of higher interest in the field of medicinal chemistry. The reactions which are difficult to carry out in conventional method are also possible in green synthetic methods like microwave irradiation. New drug candidates can also be developed using various green synthetic methods. Hence an attempt is made in this review article to bring about the merits of adopting green synthesis as an optimized method for the synthesis of Oxadiazoles.

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