Review Article

Recent Development and Green Approaches for Synthesis of Oxazole Derivatives: A Review

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This review compiles green synthetic methods intended for the synthesis of oxazole derivatives. Oxazoles are a class of compounds with a wide range of biological activities. The application and biological activity of oxazoles is highly dependent on their structure. Now-a-days, scientists have been performing the synthesis of oxazole derivatives. High demands in synthesis often result in the production of various hazardous chemical substances. So, to minimize the production of toxic chemical substances, green synthetic approaches are used in this manner. Green synthesis covers different synthetic approaches, including the application of microwave techniques, ultrasound, ionic liquids, deep-eutectic solvents, the use of catalysts and continuous flow synthesis. In this review, the authors mentioned that not only these green synthetic approaches reduce the formation and utilisation of toxic chemicals, but there is an increase in the reaction performance that enhances the product yields, purity, post-synthetic processes and energy consumption when compared to conventional methods. Due to the biological and pharmacological significance of oxazoles and the demands of decreasing toxic solvents, catalysts, and energy consumption, this article gives a full literature survey on the significance of green synthetic methods in oxazole synthesis. It contains a literature survey over the period from 2010-2020. The emphasis of this article is its comprehensive literature survey on oxazole, which is helpful for the researchers working on the oxazole scaffold and gaining information on the green synthetic approaches to their synthesis.

Key words: Oxazole, microwave assisted synthesis, green synthesis, ultrasound, ionic liquids

Heterocyclic compounds are extensively used for therapeutic purpose, research areas and industries. Heterocycle containing nitrogen and oxygen atoms are a vital class of compounds in the medicinal chemistry. The chemistry and biological activity of heterocyclic compounds has shown interest for researchers from decades and oxazole moiety has become popular in last few years considering its increasing relevance in the area of medicinal chemistry[1]. Oxazole contains two unsaturations in five membered ring including 1 oxygen atom at position 1 and a nitrogen at position 3 supported by carbons in between[2]. The structure of oxazole derivatives exerts weak interactions like hydrophobic effect, vanderwaals force, hydrogen bonds, coordination bonds, ion-dipole, pi-pi bond and so on, hence the derivatives exhibit potential application in agricultural, biotechnology, medicinal, chemical and material sciences. This review article shows the novel methods and changes in earlier studies for the preparation of oxazole. These novel methods have prepared many substituted oxazoles and thus involved in the innovation of oxazole chemistry[3].

CHEMISTRY OF OXAZOLE

In 1962 oxazole entity was firstly synthesized, but the chemistry of oxazole established in past 1876 by synthesizing 2-methyl oxazole. In the beginning of 1st world war oxazole entity came into prominence, when penicillin antibiotic was invented. During

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the invention of dienes in the Diels Alder reaction there will be new beginning of oxazole chemistry will occur[4]. Oxazole has 3 carbon, 1 nitrogen and 1 oxygen atom. These all are sp^2 hybridized and planar. The atoms also contain unhybridized p orbital which is perpendicular to the plane of σ bonds[5]. Total six non-bonding electrons are present in which 3 of carbon 1 from nitrogen and 2 of oxygen. So oxygen atom is highly electronegative, thus the delocalization is not overly effective[6]. Some basic structure derivatives of oxazole are shown in fig. 1.

Oxazole heteroatom is structurally identical to the oxygen present in furan and the nitrogen in pyridine. The studies shows that the nature of oxazole also intervene as furan and pyridine. Oxazole is basic in nature and shows similarity to those of pyridine in some aspects[7]. It shows various resonating structures shown in fig. 2.

PHARMACOLOGICAL ACTIVITIES OF OXAZOLE

Oxazole and its derivatives are used in treatment of various types of illness[8]. Oxazole shows numerous biological activities such as anti-bacterial[9,10], antifungal[11,12], agonist of free fatty acid receptor (GPR40)[13], highly selective histone deacetylase 6 (HDAC6)[14], anticancer[15,16], vegetative growth factor[17], anti-tubercular, anti-leishmanial[18], anti-protozoal[19] and anti-inflammatory[20]. Apart from these pharmacological activities, oxazole derivatives can also be used as anti-corrosive agent for stainless steel, dyes[21], anti-ageing[22], antioxidant[23], metabolism enhancing agent[24], pesticides and herbicides[6]. These compounds also involves as chelating agents for binding[25] shown in fig. 3.

Oxazoles are weak base that are employed in various chemical reactions to produce numerous biologically and therapeutically active species of organic entities[26]. Various synthetic approaches are presented in the literature owing therapeutic and physicochemical properties of oxazole derivatives. In this review, we have summarized different green approaches towards synthesis of oxazole.

CONVENTIONAL METHODS FOR SYNTHESIS OF OXAZOLE DERIVATIVES

It has been disclosed by the literature survey that there are several conventional methods available for the synthesis of oxazole derivatives, namely, Robinson-Gabriel synthesis, Fischer oxazole synthesis, van Leusen synthesis, Bredereck reaction, Cycloisomerization reaction and Erlenmeyer-Polchl reaction shown in fig. 4 and fig. 5.

Robinson Gabriel synthesis: This method synthesizes 2, 5-diaryloxazole derivatives. This is termed after the names of Sir Robert Robinson and Siegmund Gabriel, who described this reaction in 1909 and 1910 respectively[27]. The reaction mechanism shows protonation of acylamino keto moiety, into cyclization, then dehydration in presence of mineral acid, which form 2,5-disubstituted oxazole moiety. They produce low yield if cyclo-dehydrating agents are PCl_5, H_2SO_4 and $POCl_3$ etc. The yield can be increased by using polyphosphoric acid to 50-60 %[28].

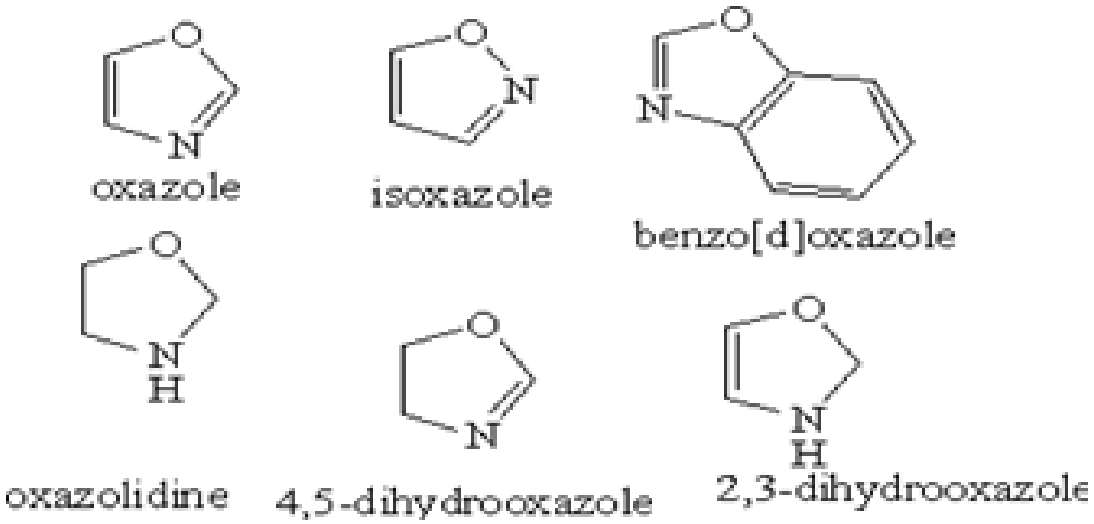

Fig. 1: Structures of oxazole and its derivatives

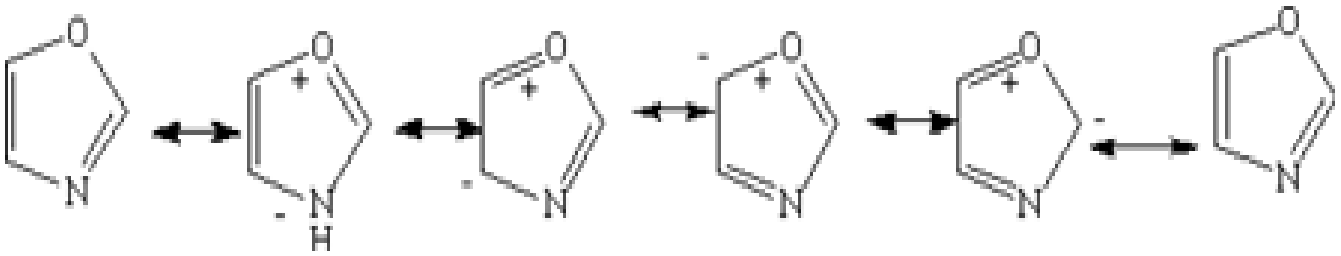

Fig. 2: Resonance structures of oxazole moiety

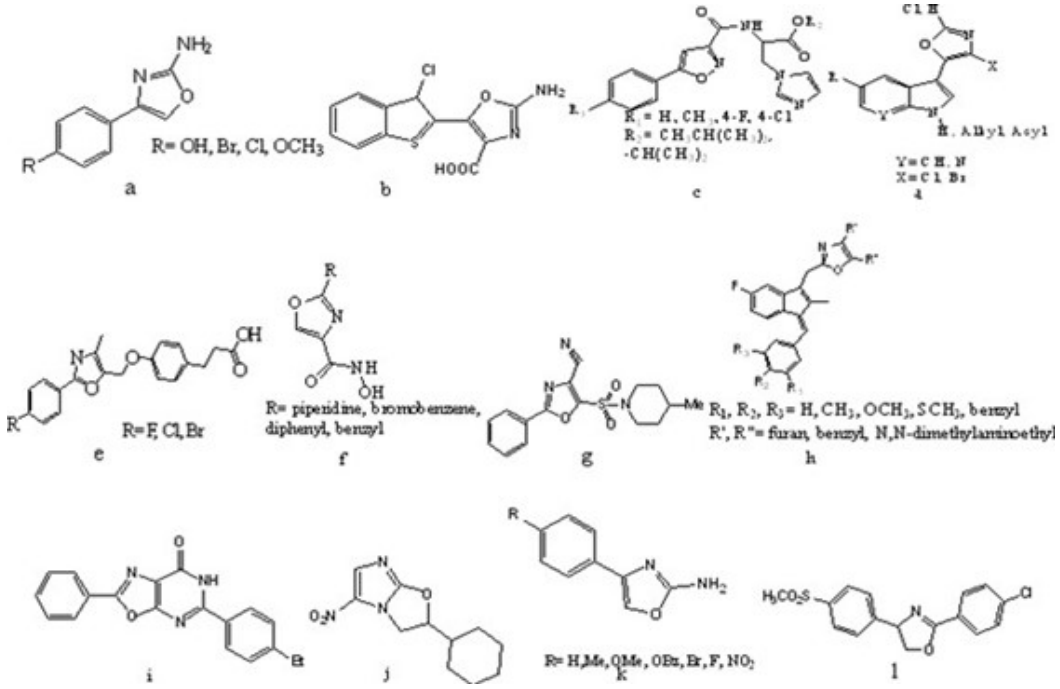

Fig. 3: Structure of some biologically active oxazole compounds; a,b: antibacterial; c,d: antifungal; e: agonist of free fatty acid receptor (GPR40); f: highly selective histone deacetylase 6 (HDAC6), g,h; anticancer; i: vegetative growth factor; j: antitubercular and anti-leishmanial activities; k: antiprotozoal and l: anti-inflammatory

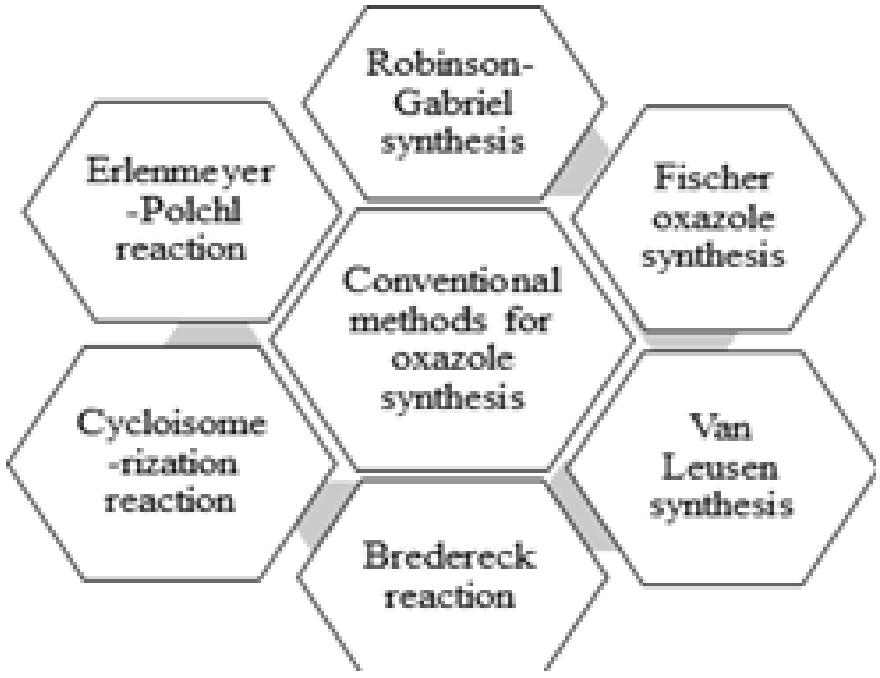

Fig. 4: Conventional methods for oxazole synthesis

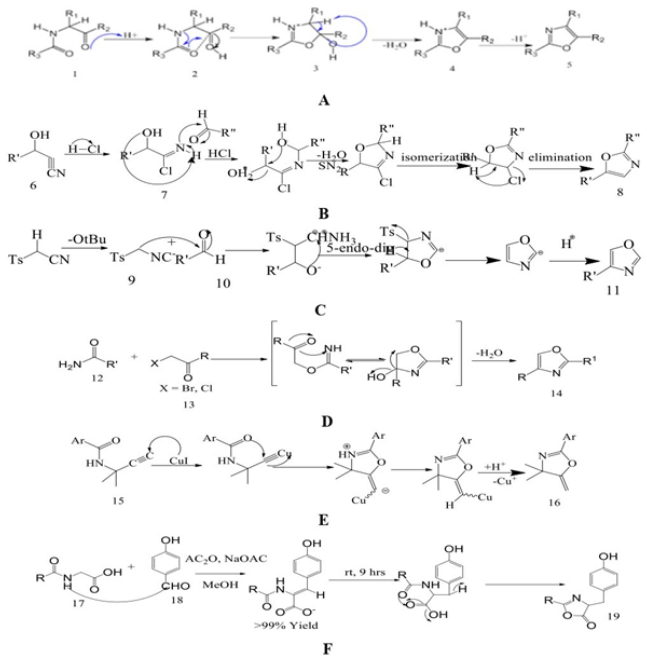

Fig. 5: Several conventional methods accessible for the synthesis of oxazole derivatives; (A): Robinson-Gabriel synthesis; (B): Fischer oxazole synthesis; (C): van Leusen synthesis; (D): Bredereck reaction; (E): Cycloisomerization reaction and (F): Erlenmeyer- Polchl reaction

Fischer oxazole synthesis: Emil fisher discovered the first synthesis for 2,5-disubstituted oxazole in 1896. This chemical synthesis occurs between equimolar amount of cyanohydrin and aromatic aldehyde in presence of dry ether and anhydrous hydrochloric acid. This is basically a dehydration reaction which occurs in mild environment due to the rearrangement of the groups[29,30].

van Leusen synthesis: van Leusen *et al.* in 1972 invented a novel chemical synthesis for oxazole ring system. He synthesizes 5-substituted oxazoles by reacting aldehyde and tosylmethyl isocyanide (TosMIC) as a precursor in a one-step reaction that takes place in mild and basic state. This process is called van Leusen synthesis. In this process, TosMIC has reactive isocyanide carbons, an active methylene group, and a leaving group. A bond will form between the hydroxyl group and the isocyano group when TosMIC is added to the aldehyde, and an intermediate will be formed as oxazoline. After the elimination of TosH, this intermediate is converted into the 5-substituted oxazole derivative[31].

Bredereck reaction: Bredereck synthesize oxazole derivatives by reacting α-haloketones with amides. 2, 4-disubstituted oxazoles can be easily synthesized by this method[32]. This is an efficient, clean and economical process for oxazole synthesis. Pei *et al.* has improved this method by using α-hydroxyketone as a starting material[33].

Cycloisomerization reaction: A versatile silica gel supported cycloisomerization reaction of easily available propargylic amide which produces polysubstituted oxazoles. This method synthesizes oxazole derivatives with high efficiency and under mild conditions. It starts with cyclization into oxazolines, then isomerization to make the oxazoles[34].

Erlenmeyer-Polchl reaction: This reaction is named after Friedrich Gustav Carl Emil Erlenmeyer, who is credited with discovering this reaction, which is used for the synthesis of oxazoles. This reaction occurs due to condensation between hippuric acid and aldehyde in presence of dry acetic anhydride and acetate ions. This prepares 2, 5-disubstituted oxazolone derivatives[35].

MODERN SYNTHETIC METHODS FOR OXAZOLES

Murru *et al.*[36] synthesize novel chiral oxazolyl alanine derivatives which finally used for preparing novel trifunctional oxazole. Oxazole ester (Boc-L-Asp-Oxz-OBn) was mixed with ethanol and ethylacetate (1:1) and treated with 10 % palladium metal on carbon support as a catalyst, then passed under hydrogen gas for 2 h. By removing Boc group with 10 ml of 55 % TFA/CH_2Cl_2 for 30 min with neutralization and coupling with free amino group and carboxylic acid, resulting in formation of new amide functions. Then washed with Dimethylformamide

(DMF) and CH_2Cl_2, and cleaved in presence of HF and washed with nitrogen gas stream to remove HF and extracted with 95 % acetic acid for 1 h, transferred to a vial and lyophilized upon freezing.

Wang *et al.*[37] prepared pyrazole substituted oxazole derivatives from pyrazole aldehyde into intermediates in presence of DMF, hydroxylamine hydrochloride under basic conditions, 4-chloromethyl-2-aryloxazole was prepared from substituted benzoic acid. In presence of thionyl chloride, it is converted into substituted benzoyl chloride using DMF as catalyst. This intermediate with ammonium hydroxide give substituted benzamide which on reacting with 1,3-dichloropropanone produced 4-chloromethyl-2-aryloxazole this on reacting with oxime and Cs_2CO_3 produces pyrazole oxazole derivatives.

Zhong *et al.*[38] designed pyrimidinamine substituted phenyl-oxazole/thiazole derivatives as potent antifungal agents. Substituted pyrimidine when reacted with substituted oxazole rings and anhydrous potassium carbonate, ethanol, and reflux for 2-4 h. Completion of the reaction was monitored in the Thin Layer Chromatography (TLC) chamber and extracted with ethyl acetate (3×80 ml).

Zhao *et al.*[39] synthesize aromatic heterocycles by use of acetophenone as starting material and treating it with diethyl oxalate in the presence of NaOEt through Claisen condensation to obtain an intermediate and performing a ring closure reaction with hydroxylamine hydrochloride to form isoxazole. By replacing oxygen from benzamide with sulphur to yield thiobenzamide and treating it with ethyl bromopyruvate by intermolecular cyclization to prepare oxazole and thiazole.

Yasaei *et al.*[40] synthesize oxazole derivatives by heating trifluoroacetic acid-ketoneamides with acid labile substituted alkoxy molecules which undergo formation of a 5-acetyl-substituted oxazole derivative. Phalke[41] added acetyl glycine, various aldehydes, anhydrous sodium acetate and acetic anhydride to the flask. Continuously stir with warming until the completion of the reaction. Heat the solution for 1 h. After completion of the reaction, cool it and leave the container overnight. The yellow crystals of oxazolone derivatives are formed (fig. 6).

MICROWAVE ASSISTED SYNTHESIS OF OXAZOLE DERIVATIVES

Mukku *et al.*[42] selected substituted aryl aldehyde, TosMIC as a starting material and added 10 ml of isopropyl alcohol in a round-bottom flask, then charged with potassium phosphate as a catalyst. Then it was irradiated in an open vessel at 800 rpm at 65° and 350 W for 8 min. The completion of the reaction is checked by TLC and cooled to room temperature. This gives a very good chance of making 4, 5-disusbtituted oxazolines and 5-substituted oxazoles.

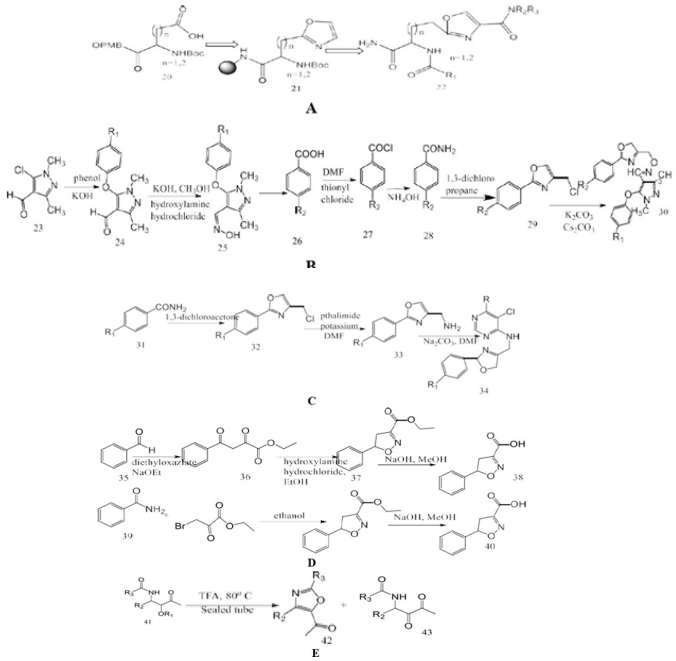

Fig. 6: Modern synthetic methods for oxazoles; (A): Chiral oxazole; (B): Pyrazole substituted oxazole; (C): Synthesis of pyrimidinamine substituted phenyl-oxazole/thiazole derivatives; (D): Synthesis of isoxazole derivatives and (E): Synthesis of oxazole using trifluoroacetic acid

Carballo *et al.*[19] synthesised and tested seven derivatives of 2-amino-4-(p-substituted phenyl)-oxazole as an antiprotozoal agent *in vitro* against *Giardia lamblia* and *Trichomonas vaginalis*. These oxazole derivatives were synthesized under microwave irradiation of a mixture of p-substituted 2-bromoacetophenone and urea in the presence of DMF.

Singh *et al.*[43] described the Suzuki reaction of 4-(4-bromophenyl)-2,5-dimethyloxazole obtained by the bromination reaction of p-bromo phenyl ethanone and further cyclisation with acetamide under microwave. This is reacted with substituted phenylboronic acid in the presence of bis (triphenylphosphine) palladium, chloride, potassium and DMF, which produce novel 2,5-dimethyl-4-substituted biphenyl-1,3-oxazole derivatives in a good yield and are evaluated for *in vitro* antimicrobial activity.

Hafez *et al.*[44] synthesized novel pyrazole derivatives having pyran, pyridine, pyrazole, imidazole, 1,3-oxazole and 1,3,4-thiadiazole moiety. 4-disubstitutted imidazolyl-3-methyl- 1-phenyl1H-pyrazole derivatives has been synthesized under microwave irradiation by reacting 1,2-diaryldiketones and 3-methyl-1-phenyl-1H-pyrazole-4-carboxaldehyde in the presence of 2-aminoethanol with pyridinium hydrobromide perbromide as a catalyst in water afforded 2-(3- methyl-1 phenyl-1H-pyrazol-4-yl)-4,5 dihydro-1,3-oxazole.

Kumar *et al.*[45] react aromatic ketone, thiourea/urea and iodine in an open vessel, place it in a microwave cavity and irradiated it at 50 W (140°) for 10 min. After the completion of reaction, the reaction mixture is cooled to 70° and affords the 2-aminooxazole derivatives.

Rajaguru *et al.*[46] reported synthesis of oxazole derivatives by reacting α-azidochalcone with trifluoroacetic acid in dry two-neck round bottom vessel fitted with a calcium guard tube and a magnetic bar and then gradually heated to a higher temperature in the microwave for 30 min. The reaction is monitored by TLC using petroleum ether/ethyl acetate (8:2) as a solvent to yield oxazole derivatives.

Rostamizadeh *et al.*[47] synthesized azalactones using microwave assisted Erlenmeyer synthesis. Reaction of hippuric acid and substituted aldehyde or ketone with acetic anhydride and MgO/Al_2O_3 as a catalyst in the microwave oven. The progress of the reaction is checked by TLC and cooled to room temperature in hot ethanol (2:1) added to it and stirred for 15 min. Then the catalyst is separated by decantation to afford the final product as an azalactone.

Mollo *et al.*[48] examined the cyclization reaction of N-benzoylaminoethanol with PPE/$CHCl_3$ in an open-vessel microwave reactor for 8 min at 70° in reflux, which led to the synthesis of 2-phenyl-2-oxazolines with an excellent yield of 88 %. On the other hand, using a closed vessel, the yields increased to 95 %. Rahman *et al.*[49] synthesised diastereoselective hexahydropyrrolo[2,1-b]-oxazoles. On reacting pyrrolidine and 4-chlorobenzaldehyde as substrates under microwave irradiation in toluene for 15 min, the final diastereomer oxazole with two phenyl groups in trans form.

Kadagathur *et al.*[50] establish the construction of a novel series of 2-aminobenzoxazole derivatives. This includes reactions between o-amino phenol and phenyl isothiocynante using various oxidants under different reaction conditions such as changing temperature and reaction time. To begin, the reaction is carried out in a microwave with ethanol as the solvent and no oxidant to produce the final product of N- phenylbenzo[d]oxazol-2-amine.

Ziarani *et al.*[51] investigate the synthesis of novel benzoxazole derivatives by performing a condensation reaction between 2-amino-3-hydroxypyridine and benzoyl chloride using Santa Barbara Amorphous-15 (SBA-15) as a basic nano-catalyst in microwave irradiation and solvent free conditions. This reaction proceeds in two ways by using DMF as solvent at optimum temperature in the presence of SBA-15, resulting in the formation of N-(3-hydroxy-2-pyridyl) Benzamide and substituted benzoic acid as an intermediate. Then, using the same reagents under microwave at room temperature, this gives 2-aryloxazolo-[4,5-b] pyridine as a final product (fig. 7).

SYNTHESIS OF OXAZOLES USING VARIOUS CATALYST

Ueda *et al.*[52] described an efficient, safe, and novel benzoxazole synthesis using a copper catalyst $[Cu(OTf)_2]/O_2$. The reaction of substituted benzanilides in the meta or ortho position with electron donating alkyl or alkoxy groups yielded the corresponding benzoxazole with a high yield.

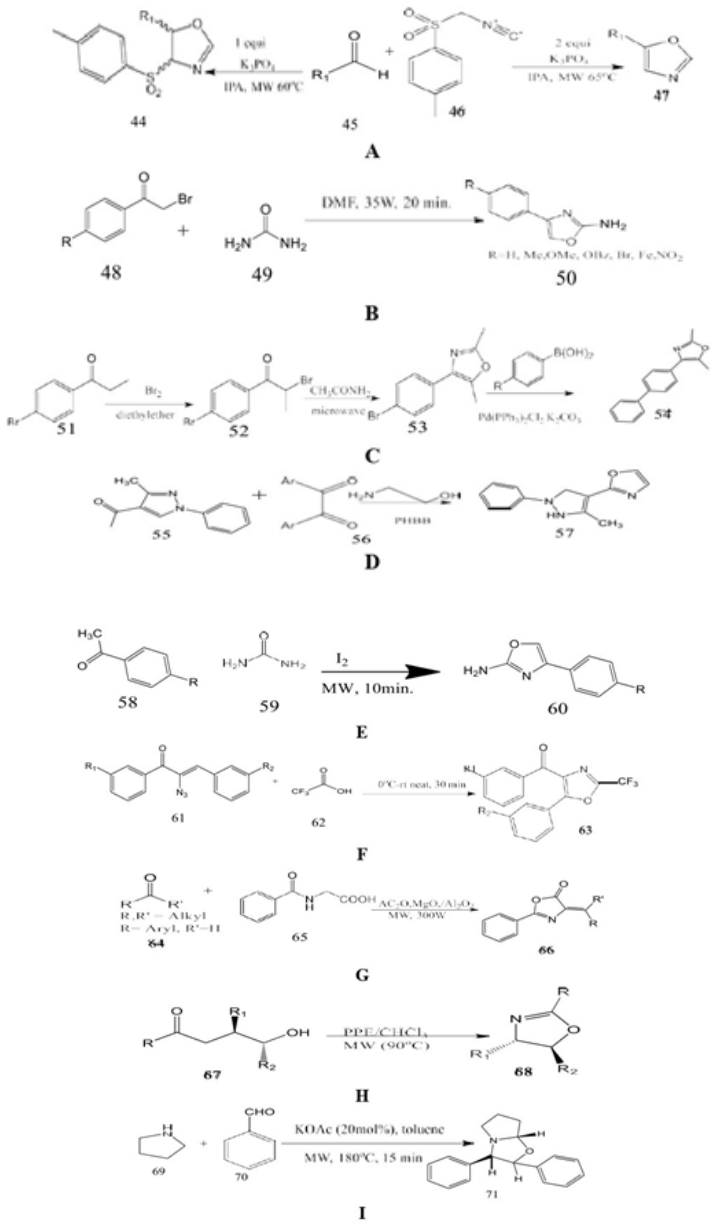

Fig. 7: Microwave assisted synthesis; (A): Two component [3+2] cycloaddition reaction; (B): Synthesis of derivatives of 2-amino-4-(p-substituted-phenyl)oxazole; (C): Suzuki reaction; (D): Pyrazole derived oxazole molecules; (E): 2-aminooxazole derivatives; (F): Oxazole synthesis using MW irradiation; (G): Erlenmeyer synthesis of azalactones; (H): Cyclisation reaction and (I): Diastereoselective synthesis of hexahydropyrrolo[2,1-b] oxazole derivatives

Tomi *et al.*[53] have developed a novel multistep synthesis for oxazole and benzoxazole derivatives. Firstly, glycine is treated with 4-methoxy benzoyl chloride in a NaOH solution to give 4-methoxy hippuric acid. Then it is reacted with an equal quantity of ethyl chloroformate in the presence of N-methylmorpholine in CH_2Cl_2 to produce 2-(4-methoxyphenyl)-5-oxazolones. This azlactone with excess toluene and anhydrous $AlCl_3$ at room temperature gives 2-aza-1-(4-methoxyphenyl)-4-toluel-1,4-butandiones. Then reflux with phosphorus oxychloride for 48 h to give 2-(4-methylphenyl)-5-(4-methoxyphenyl)-1,3-oxazole.

Kumar *et al.*[54] performed a two-step synthesis for 2-phenyl-4,5-substituted oxazoles using copper as a catalyst. The reaction involves the nucleophilic ring opening of the 4- bis(methylthio)methylene-2-phenyloxazole-5-one template to reduce N-benzoyl--bis(methylthio)enamide. These enamide derivatives are successively changed into 2-phenyl-5-(methylthio)-4-alkoxycarbonyl/amido/acyloxazoles by using silver carbonate as a catalyst, forming the 5-endo cyclization.

Gao *et al.*[55] synthesized oxazole in the presence of iodine and potassium carbonate in DMF at 80°

using bromoacetophenone and benzylamine as starting reagents to give 2,5-diphenyloxazole in the 46 % yield. Reddy *et al.*[56] describe an easy and convenient synthesis of 2,4-disubstituted oxazoles by coupling substituted α-diazoketones with substituted amides in 1,2- dichloroethane in the presence of copper(II) triflate [$Cu(OTf)_2$].The desired product, 2,4-disubstituted oxazole, is obtained at an 87 % yield after increasing the temperature from 25° to 80°. Bailey *et al.*[57] identified the optimal reaction conditions for the synthesis of 2,4-disubstituted and 2,4,5-trisubstituted oxazoles by using haloketones and substituted arylamides in the presence of ethyl acetate and silver triflate (AgOTF) as a catalyst used for promotion of cyclization reaction, observing the effect of temperature, stoichiometry, and optimum light on the process.

Hu *et al.*[58] explored several cyclization reactions of propargylic amides, because of their rapid association of structural complexity and functional group similarity, in the recent years this method has gained consideration. The reaction is effectively attained with the help of various transition metals, Bronsted acid, Lewis acid, halogens, strong base, non-transition metals and catalyst mediated cyclization.

Yamada *et al.*[59] developed a novel synthetic method for the synthesis of trisubstituted oxazoles through a one-pot oxazole synthesis/Suzuki-Miyaura coupling. In this reaction, carboxylic acid, dehydrative condensing agent, amino acids and (4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methyl-morpholinium chloride) are used. In the presence of a Ni catalyst, Suzuki-Miyaura coupling with boronic acids produces a resultant 2,4,5-trisubstituted oxazole with excellent yield. Regalla *et al.*[60] aimed at the synthesis of 2,4-disubstituted oxazole using palladium/copper as a catalyst by direct arylation. This has been synthesised by reacting 4-substituted oxazole with aryl bromide in the presence of potassium hydroxide, CuI and Pd $(PPh_3)_4$ in dimethoxyethane (fig. 8).

ULTRAOSUND ASSISTED SYNTHESIS OF OXAZOLES

Singh *et al.*[61] described a novel synthesis of oxazole derivatives through Ultrasound (US) and Deep Eutectic Solvent (DES). As the reaction between 4-substituted phenacylbromide and amide derivatives goes on, DES are added and stirred for 3-5 min. Then TLC is used to check the reaction at 65°. This is then

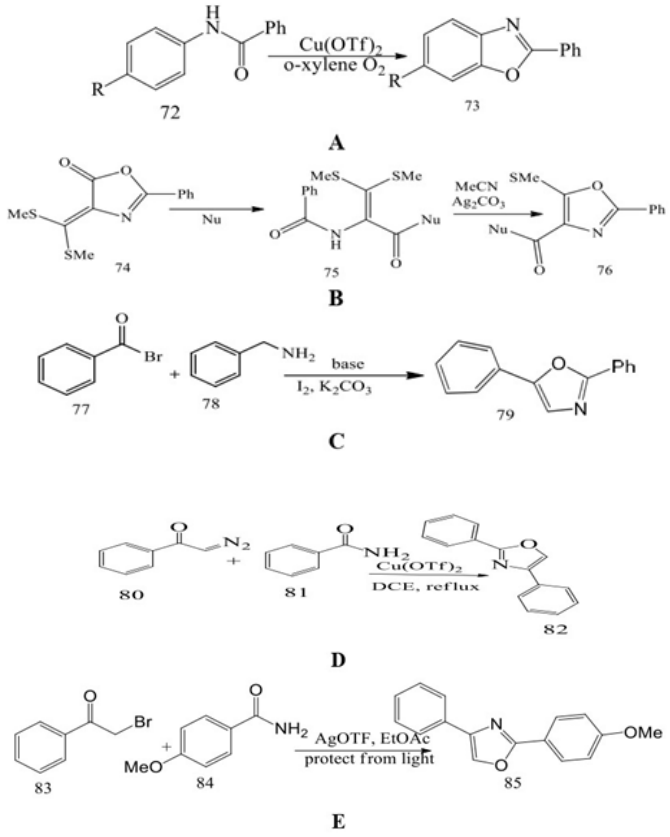

Fig. 8: Synthesis of oxazole using catalyst; (A): Benzoxazole synthesis using copper catalyst; (B): Synthesis of 2-phenyl-4,5-substituted oxazoles using copper as a catalyst; (C): Synthesis of diphenyl oxazole; (D): Oxazole synthesis using copper(II) triflates catalyst and (E): Synthesis of diaryl oxazole using silver triflate as catalyst

extracted with dichloromethane (DCM).

Naeimi *et al.*[62] presented an easy and effective technique for one-pot synthesis of 2-arylbenzoxazoles, which are promptly synthesised from a mixture of o-aminophenol and aromatic aldehyde or heteroaromatic aldehyde using MWCN held KCN in DMF using ultrasound irradiation with a power of 60 W at 55 % amplitude and at a frequency of 20 kHz for a range of 12-650 s. For the completion of a reaction, TLC is used. The product benzoxazole was characterised by the spectroscopic data.

Nikpassand *et al.*[63] investigated a green approach by using ultrasound for the environmentally friendly and safer synthesis of benzoxazole derivatives. The mixture of azo-linked substituted salicylic acid with different quantities, 1.14 gm of 2-amino-4-chlorophenol and 10 ml of ethanol is added to a Pyrex glass open vessel and irradiated with ultrasound in a water bath under silent conditions at room temperature.

Kaur *et al.*[64] illustrate the synthesis of various heterocyclic compounds using the ultrasonication method due to its short reaction time, high yield and mild reaction environment. After 30 min of ultrasonic irradiation, a reaction occurs between benzonitrile and 2-aminoethanol and is mixed with $InCl_3$ to synthesise 2-phenyloxazoline with excellent yield.

Nikseresht *et al.*[65] performed reaction between 5-amino-4-cyano-2-phenyl-1,3-oxazole, cyclohexanone and activated $[Cu_3(BTC)_2]$ and heated for 353 K for 2 h. The mixture is placed in an ultrasonic bath and irradiated at room temperature (20-25°). Completion of the reaction is monitored by TLC 1:2 (EtOAc/n-hexane as eluent). This method is easy, efficient, and environmentally friendly for synthesising tacrine analogues in the presence of [Cu3(BTC)2] as a catalyst.

Abdolmohammadi *et al.*[66] synthesis of 1,3-oxazole and 1H-pyrolo-[1,3]-oxazole, both of which are effective antioxidants with high yield. To the solution of alpha bromoketone, add acid chloride by magnetically stirring, ammonium thiocyanate, NaH, and Fe_3O_4 Magnetic Nanoparticles (MNPs) in 5ml of water at 50° for 30 min from the start of the reaction. Afterwards, the 1,3-oxazole solution is magnetically stirred, then activated acetylenic compound and piperidine in 5 ml of DCM are added. Then a solution of alpha-bromoketone and activated acetylenic compound by magnetically stirring with Fe_3O_4 MNPs for about 10-20 min with the stirring.

Kandula *et al.*[67] used 2-Iodoxybenzoic acid as an oxidant in dimethyl sulfoxide at 30° in the presence of air under ultrasound irradiation to perform the domino reaction of benzoin and substituted benzylamine due to its advantages over conventional methods. It produces a compound with an excellent yield. This 2,4,5-trisubstituted oxazole is synthesized by this method (fig. 9).

CONTINUOUS FLOW SYNTHESIS OF OXAZOLES

Glockner *et al.*[68] focused on continuous flow synthesis using Deoxo-Fluor, resulting in more than 99 % conversion of β-hydroxy amides to the oxazolines. These fluorinated compounds resulted in the synthesis of a larger number of unwanted by-products. A solution of β-hydroxy amides (0.25 M) and deoxo-fluor at a flow rate of 3.00 ml/min is combined at a T-piece before passing into a reactor coil at 25° Then sodium bicarbonate solution is added at a T-mixer to quench any residual hydrogen fluoride and then directed in to a Zaiput liquid-liquid membrane separator.

Bay *et al.*[69] performed the reaction of alkylideneoxazolines with molecular oxygen in a micro structured reactor to enhance safety and provide a significant application for synthesis. The synthesis of oxazole-hydroperoxide is carried out using flow conditions using starting compounds like oxazolines at temperatures ranging from 70° to 100° at two varying pressures (1 and 18 bar). This oxazoline is mixed with reagent AIBN, n-dodeacne and the solvent 2-methoxy ethylacetate in a microstructured reactor containing the PTFE-T-mixer.

Rattanangkool *et al.*[70] screened the photoredox catalysis through an amination reaction between 2-mercaptobenoxazole and n-butylamine through irradiation using white light-emitting diode. The reaction is carried out in the presence of a transition metal photoredox catalyst, $Ru(byp)_3Cl_2$, which results in a lower yield of benzoxazole, sulfenamide and disulphide product. So, to enhance the yield, we can use both Rose Bengal and EosinY, which give an excellent yield. In recent years, continuous flow synthesis has gained attention in organic synthesis

as it is safer, more efficient, waste reduction and requires fewer solvents.

Rossa *et al.*[71] developed a three-step synthesis of vinyl azides in a continuous flow reactor containing a Perfluoroalkoxy coil immersed in a silicon bath at 150°. The vinyl azide solution in acetone is delivered into the reactor using a syringe pump to generate azirines under nitrogen gas generation, which is then reacted with bromoacetyl bromide in the reaction vessel placed between the reaction zones to remove excess nitrogen to yield 2-(bromomethyl) oxazoles.

Bracken *et al.*[72] performed a two-step synthesis of claisen condensation between acetophenones and diethyl oxalate to form 1,3-dicarbonyls, which were treated with hydroxylamine hydrochloride in a thermal cyclocondensation process to produce isoxazole with excellent yield. This compound undergoes further reaction under the vapourtec E-series module at a flow rate of 0.5 ml/min. Different solvents have been used, like DCM, acetone, tetrahydrofuran and ethanol. Temperatures should be kept between 25-45° and nitrogen gas should be used to produce oxazole.

Ramanjaneyulu *et al.*[73] created a flow synthesis by reacting benzo[d]oxazole-thiol and benzhydryl bromide as starting materials in reactor vessels

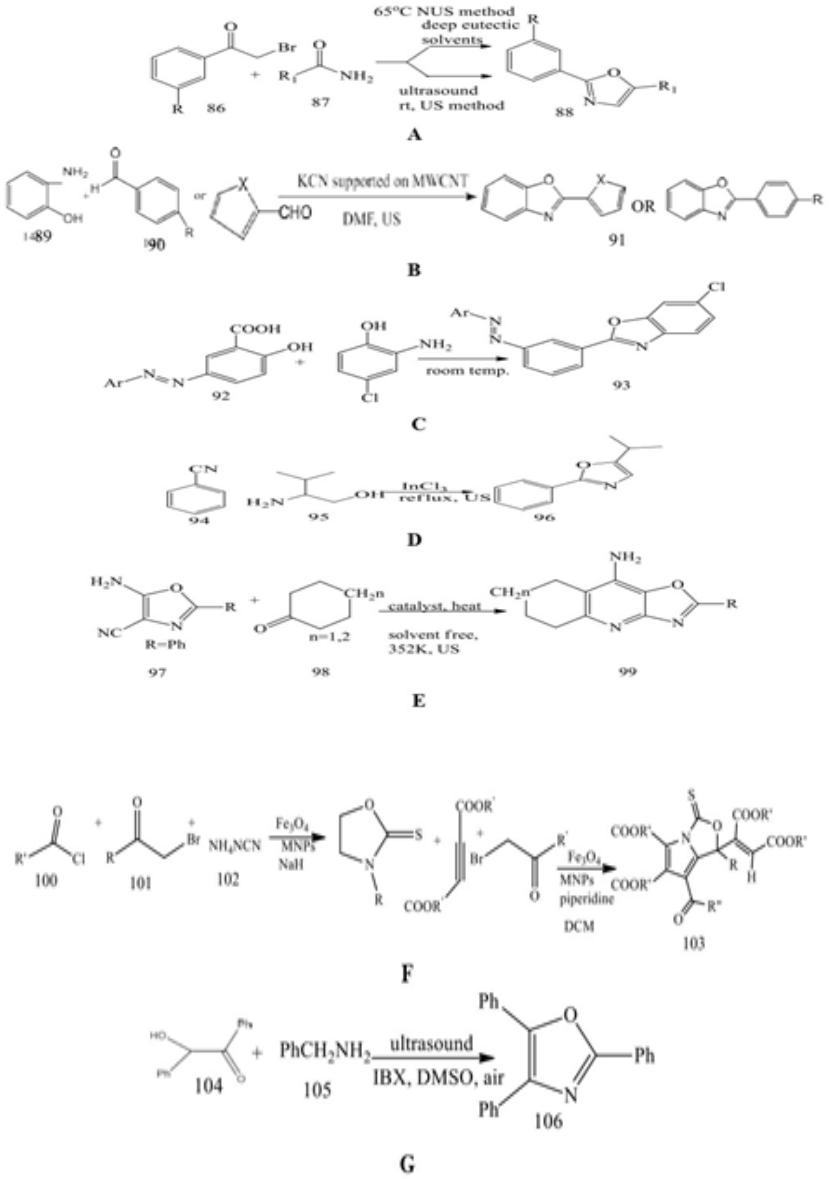

Fig. 9: Oxazole synthesis through ultrasound method; (A): Using deep eutectic solvents; (B): One pot synthesis of 2-arylbenzoxazole; (C): Synthesis of benzoxazole derivatives; (D): Ultra sonication method for synthesis of oxazole derivative; (E): Tacrine analogue synthesis; (F): Synthesis of 1,3-oxazoleand 1H-pyrolo-[1,3]-oxazole using ferric oxide magnetic nanoparticles (MNPs) and (G) Ultrasound irradiation for synthesis of 2,4,5-trisubstituted oxazole

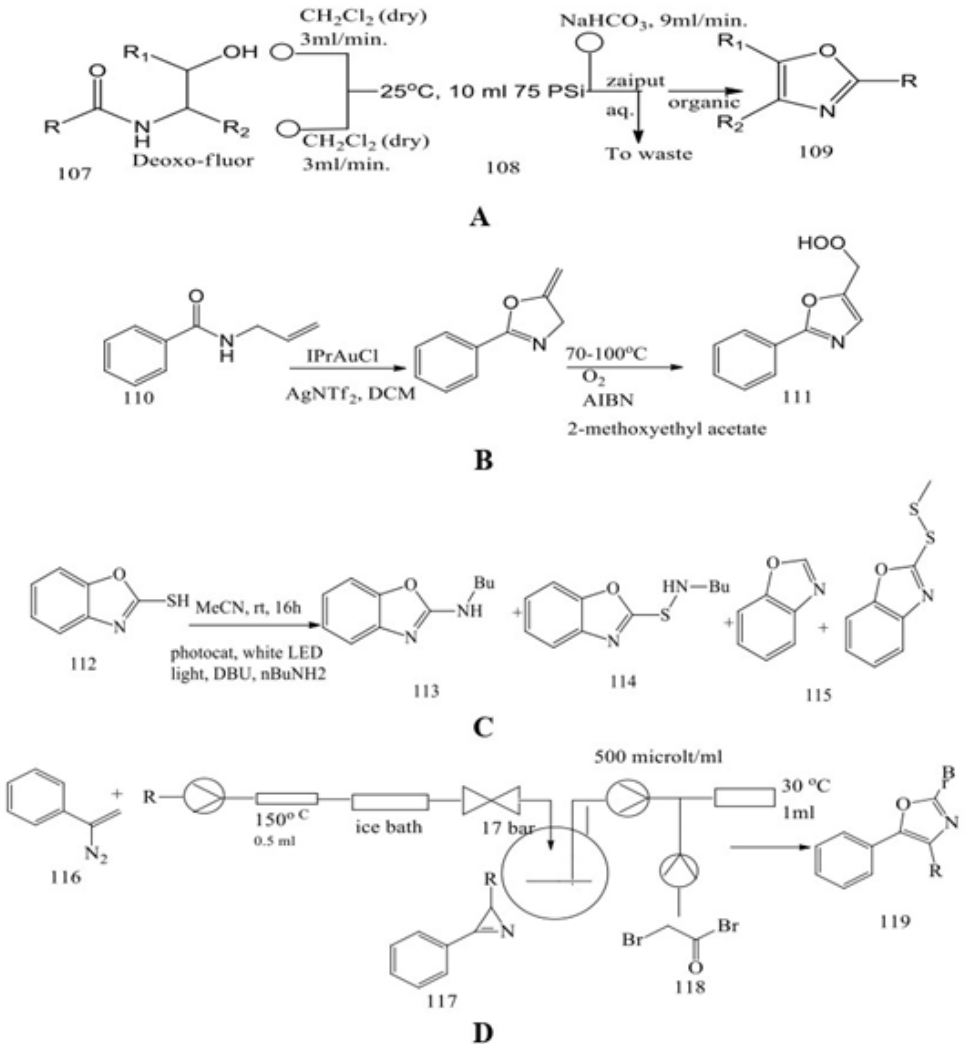

Fig. 10: Continuous flow synthesis of oxazoles; (A): Conversion of β-hydroxy amides to oxazolines using Deoxo-Fluor; (B) Synthesis of oxazole-hydroperoxide using flow conditions; (C): Benzoxazole synthesis using photo catalyst and (D): Three step synthesis of 2-(bromomethyl)oxazoles in continuous flow reactor

with litium thiolate species. This forms a reacting intermediate which, on reaction with n-BuLi and using two T-micromixers M1 and M2, forms a desired product with good yield (fig. 10).

SYNTHESIS OF OXAZOLES USING IONIC LIQUIDS

Wu *et al.*[74] prepared novel oxazoles using advanced one-pot van Leusen synthesis in ionic liquids. The oxazoles were synthesized from TosMIC with aliphatic halides, [bmim] Br as solvents and aldehydes, which produced a high yield of products. This ionic liquid can also be reused up to six times without any loss of yield.

Miao C *et al.*[75] synthesized novel benzoxazole derivatives using metal-free and efficient long-chained acidic ionic liquids. It involved intermolecular cyclisation of 2-amino phenol with 2, 4-pentanedione in the presence of ionic liquids to synthesise benzoxazole. The long-chained ionic liquids such as [BsMeP] [OTf] and [BsHDP] [OTf] are better than simple ionic liquids showing micellar action and surfactivity and could be recycled at least six times.

Azizi N *et al.*[76] performed one-pot synthesis using DES as an ionic liquid to synthesise 2-aminooxazole and 2-aminothiazole derivatives. This includes a one-pot three-component reaction between urea or thiourea, active methylene compounds and N-Bromosuccinamide (NBS) using DES as an effective catalyst to produce 2-aminooxazole and 2-aminothizole with excellent yield in mild reaction conditions.

Abonia R *et al.*[77] synthesized oxazole derivatives using imidazolium as an ionic liquid in the Suzuki

Pd-mediated C-C coupling mechanism along with Piperidine-Appended Imidazolium [PAIM] [NTf2] ion as a specific ionic liquid Previously synthesised oxazoles and imidazoles are obtained *via* van Leusen synthesis and subjected to Suzuki Pd-catalyzed C-C coupling reactions. This mechanism is highly effective for synthesising imidazole and oxazole compounds with good yield.

Miao C *et al.*[78] synthesis of oxazole derivatives using pyrrolidine-derived long-chain ionic liquids. This synthesis involves the thiolation of alcohols to prepare variouscompounds containing a thioether moiety. The ionic liquids are more effective than common ionic liquids containing imidazole, providing 99 % yield with [BsCtP] [OTf] as a catalyst. This catalyst is widely applicable for the reaction of aromatic alcohol with aliphatic thiols and aromatic thiols such as benzothiazole-2-thiols and benzoxazole-2- thiols.

Cheng *et al.*[79] investigated one-pot synthesis for the preparation of 4-aryl2-phenyloxazoles by performing cyclocondensation of benzamide with [(2,4-dinitrobenzene) sulfonyl]oxy molecule in the presence of [Bmin] [PF6] at 80°. As shown in scheme 58, the ionic liquid in this reaction plays a very important role both as solvent and promoter and can be easily recovered and reused without any loss of activity.

Zhou *et al.*[80] focused on direct oxidative amination using ionic liquids as catalysts for benzoxazoles at room temperature and metal-free conditions. This oxidative amination reaction is carried out under mild catalytic states between several derivatives of benzoxazoles and secondary amines to give substituted benzoxazole derivatives. The use of ionic liquid [BPy] is inexpensive and eco-friendly and can be recycled and reused more than four times without any loss of catalytic activity.

Muthyala *et al.*[81] performed a novel and highly effective one-pot synthesis for 2,4- disubstituted thiazoles and oxazoles from substituted ketone derivatives and reacting with amides/urea and thiamides/thiourea using phenyltrimethylammonium bromide (PTT) as an *in situ* brominating agent under [bmim] [BF4] as an ionic liquid. This procedure

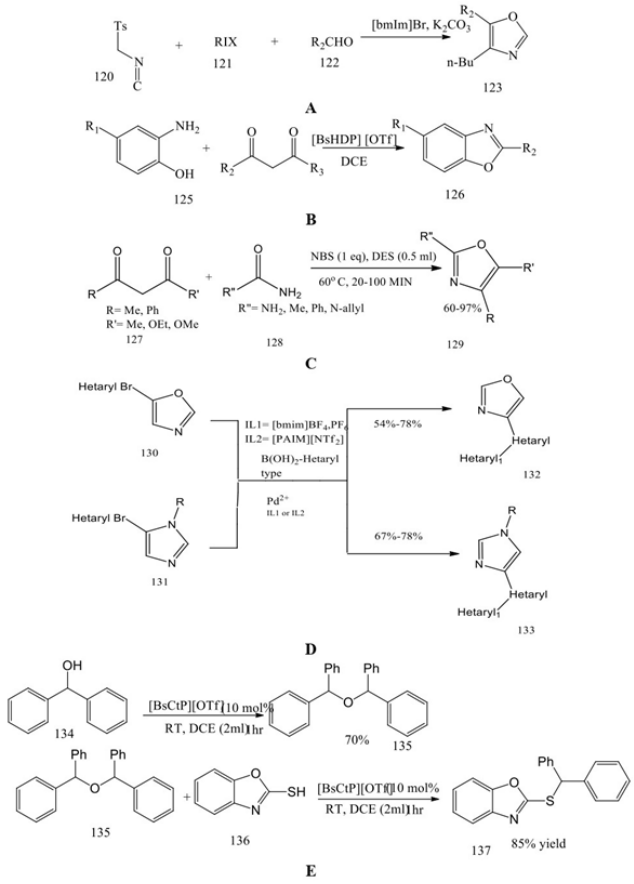

Fig. 11: (A): Synthesis of oxazole using ionic liquids; (B): Benzoxazole synthesis using long chained acidic ionic liquids; (C): Oxazole synthesis using deep eutectic solvents and ionic liquids; (D): Synthesis of oxazole and imidazole *via* Suzuki Pd-mediated C-C coupling mechanism using [bmim] BF4,PF6 and [PAIM][NTf2] as ionic liquids and (E) Thiolation of alcohol using pyrrolidine derived catalyst for the synthesis of benzoxazoles

has great advantages over other methods due to the avoidance of hazardous organic chemicals, the handling of lacrymetric solvents, and the toxic catalyst (fig. 11).

CONCLUSION

This pioneer literature reveals the importance of oxazole as a conversant nucleus, showing immense potential for the advancement of potent novel chemical entities retaining anti-inflammatory, antidiabetic, antiviral, antibacterial, anticancer, analgesic, and antihypertensive activity. This article also studied various synthetic pathways and reactions undergoing oxazole and its derivatives. Finally, different synthetic methods have been studied for the synthesis of di-substituted and tri-substituted oxazole derivatives through multicomponent reactions shown in different literature sites, which have been presented in this review article. Through various literature surveys, we have summarized all the multicomponent synthesis of the oxazole moiety using different methods, which include conventional methods, microwave assisted techniques, catalytic synthesis, and ultrasound-assisted synthesis. Overall, this review summarizes various green methods for the synthesis of oxazole and its derivatives.

Conflict of interests:

Authors declare that there is no conflict of interest.

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