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Structure: Mechanistic Studies and Pharmacological Importance of Oxadiazole Derivatives and Allied Oxygen Heterocycles

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ABSTRACT

Oxadiazole is a five-membered heterocyclic compound containing two carbon, two nitrogen, and one oxygen atom in the ring. 1,3,4-oxadiazole is widely investigated because of its significant interacting potential with distinct binding sites in the biological systems.A range of 2-substituted phenyl -1, 3, 4-oxadiazole-2- thion derivatives(2) of pharmacological interest have been synthesisized from substituted carboxylic acids (1). Pyridine carboxylic acids (3) have also been transformed to 5-pyridyl-1, 3, 4-oxadiazole-2-thion derivatives (4) in excellent yields. Ɣ-lactones are oxygen containing heterocycles extensively distributed in nature and display a broad spectrum of biological activities.Avariety of gama lactones have been generated from epoxides and esters .Oxygen heterocycles of the type (6) possessing antitumor properties have been obtained from alkenyl ketones in high yields. Mechanistically interesting NBS mediated cyclisations of two delta-alkenyl ketones, (7) and (8) have been employed to afford stereoisomer's (9) and (10). This article presents newly developed mechanisms for the construction of a range of oxadiazole derivatives and allied oxygen heterocycles. Recent applications of pharmacological importance of these compounds have also been added.

Keywords: Oxadiazole; Oxygen heterocycles; Mechanism; Pharmacological; Lactones; Applications

INTRODUCTION

Oxygenated heterocycles are probably the most common structural motifs spread across natural products. Their stereoselective preparation has become a continuous challenge for synthetic organic chemists due to the remarkably rich array of functionalities and chiral centres [1-5]. Acid-catalyzed cyclisations of hydroxy epoxides have been employed for the stereoselective construction of tetrahydropyrans [6]. Catalytic methodologies based on the olefin activation are dominated by the palladium chemistry, which has attained distinguished levels of maturity. [7,8] In this field, the construction of heterocycles proceeds through carbon-carbon or carbon- heteroatom bond formation, depending upon the nucleophile involved in the ring-closure step. The synthesis of pyrans depends on the intramolecular cyclization of hydroxy alkenes, which suggests the satisfactory activation of the olefin with a palladium catalyst and the subsequent intramolecular attack by the alcohol. Aldol products obtained from beta-keto esters can participate in an acid-catalyzed Knoevenagel condensation resulting a highly reactive α, β-unsaturated keto ester, which subsequently undergoes a 6-endo-trig cyclization based on a reversible oxa-Michael addition. Decarboxylation of the resultant system provides the 2,6-cis-disubstituted tetrahydropyranones[9,10].This approach has been employed for the synthesis of (±)centrolobine.1,3,4-oxadiazole is widely investigated dueto its remarkable interacting potential with diverse binding sites in the biological systems [11]. Its derivatives have been reported to possess different pharmacological activities like anticancer, antimicrobial, antihypertensive, anticonvulsant, and anti-inflammatory agents. Furthermore, 1,3,4-oxadiazoles analogues represent a unique metabolic study and hydrogen bonding ability, which further manifests its medicinal importance (12-16).

LITERATURE REVIEW

Ɣ-lactones are widely distributed in nature and display broad biological and cytostatic properties making them interesting lead structures for drugs [17]. The synthesis of Ɣ-lactones has been carried out from butenolides by catalytic hydrogenation. Chiral catalysts have been a focus for enantioselective hydrogenation of most research works in the recent past [18-23]. Reduction of 3-halo or 3-phenylselenyl butyrolactones has been carried out by nickel chloride/sodium borohydrides leading to the elimination of the halide or phenylselenyl group [24]. Reduction of succinic

anhydrides, NaBH4 or Li(t-BuO)3AlH results the formation of ɣ- lactones but the regioselectivity process cannot be controlled [25,26]. Highly functionalized tricyclic heterocycles have been obtained by the diastereoselective Diels-Alder cycloadditions of masked o-benzoquinones with furans which can be subsequently transformed into tricyclic ɣ-lactones by oxidation with NaIO4 [27]. The traditional method for the preparation of ɣ-lactone rings from a preformed hydrocarbonated chain starts from an acid derivative with an X group in the ɣ-position. Cyclization from ɣ-hydroxyacids by acid [28-31] or enzimatic [32] treatment has been used for the synthesis of a range of natural products. ɣ -lactones can also be obtained by a simple oxidation process from lactol acetals [33-38], or from free or protected 1,4-diols [39-43]. The routine oxidants employed are Jones reagent, TPAP, PCC or NaIO4, but in certain cases, ruthenium catalyst [44,45], TEMPO/NCS/R4NI [46,47] or the enzymatic process [48] have also been used.

In this article we have developed mechanism for a series of oxadiazoles, lactones and allied oxygen heterocycles, Although the compounds are known but the proposed mechanisms are quite unknown as revealed by the exhaustive literature survey. Alongside, a broad spectrum of applications of pharmacological importance have also been incorporated in this article.

DISCUSSION

Oxadiazoles are five-membered heteroaromatic rings occurring frequently in drug like molecules and exist in different regioisomeric forms. The most stable isomeric structure among all isomeric oxadiazoles is unsubstituted 1,3,4-oxadiazole. Literature is full of references citing its reactions with a variety of substrates and yielding a wide range of products of both pharmacological and mechanistic interest.1,3,4-oxadiazoles possess biological activity and their derivatives are used in medicine and pharmacology, as well as in agriculture [49]. 2-thione-1,3,4-oxadiazole derivatives (2) have been synthesized in excellent yields from the corresponding substituted carboxylic acids (1) in different steps using ethanol and acidic catalysts (Figure 1).

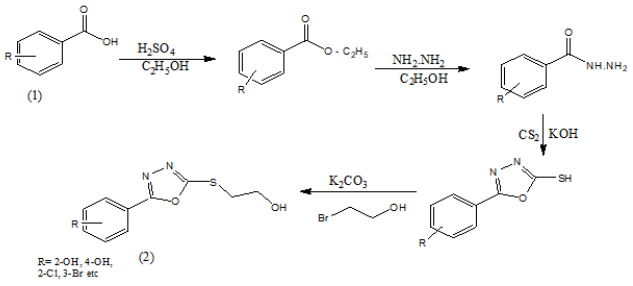

Figure 1: Synthesis of 2-substituted phenyl -1, 3, 4-oxadiazole-2-thion derivatives.

Literature survey reveals that the mechanism of formation for the compound (2) has not been suggested earlier, therefore the most plausible mechanism proposed for the formation of 2-substituted phenyl -1, 3, 4-oxadiazole-2- thion derivatives (2) is depicted as below Figure2

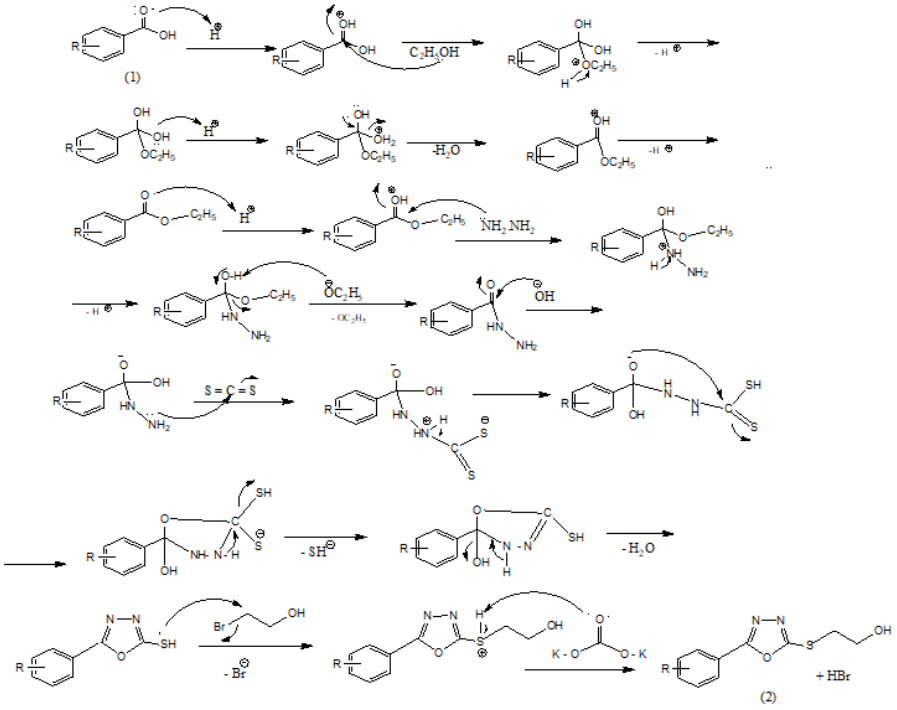

Figure 2: Mechanism developed for the formation of 2-substituted phenyl -1, 3, 4-oxadiazole-2- thion derivatives (2).

In a similar reaction 5-pyridyl-1, 3, 4-oxadiazole-2-thion derivatives (4) have been synthesized from acid substituted pyridine rings (3) in good yields (Figure 3).

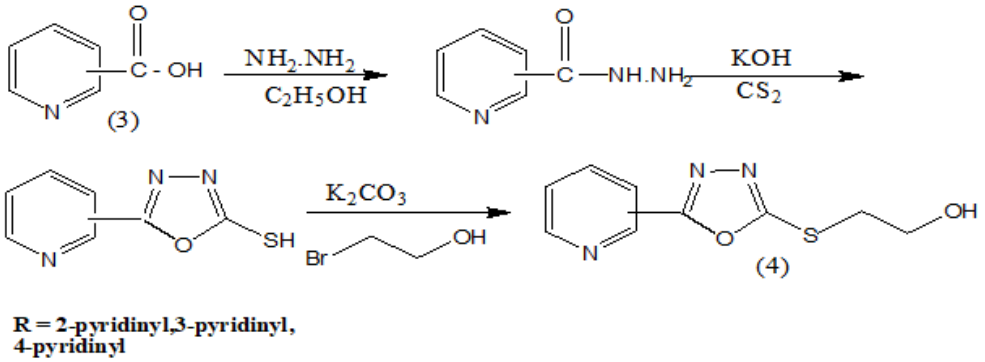

Figure 3: Synthesis of 5-pyridyl-1, 3, 4-oxadiazole-2-thion derivatives (4)

As disclosed by literature survey, mechanism has not been developed earlier for the formation of compound(s) (4), therefore the possible mechanism suggested for its formation is discussed below Figure 4.

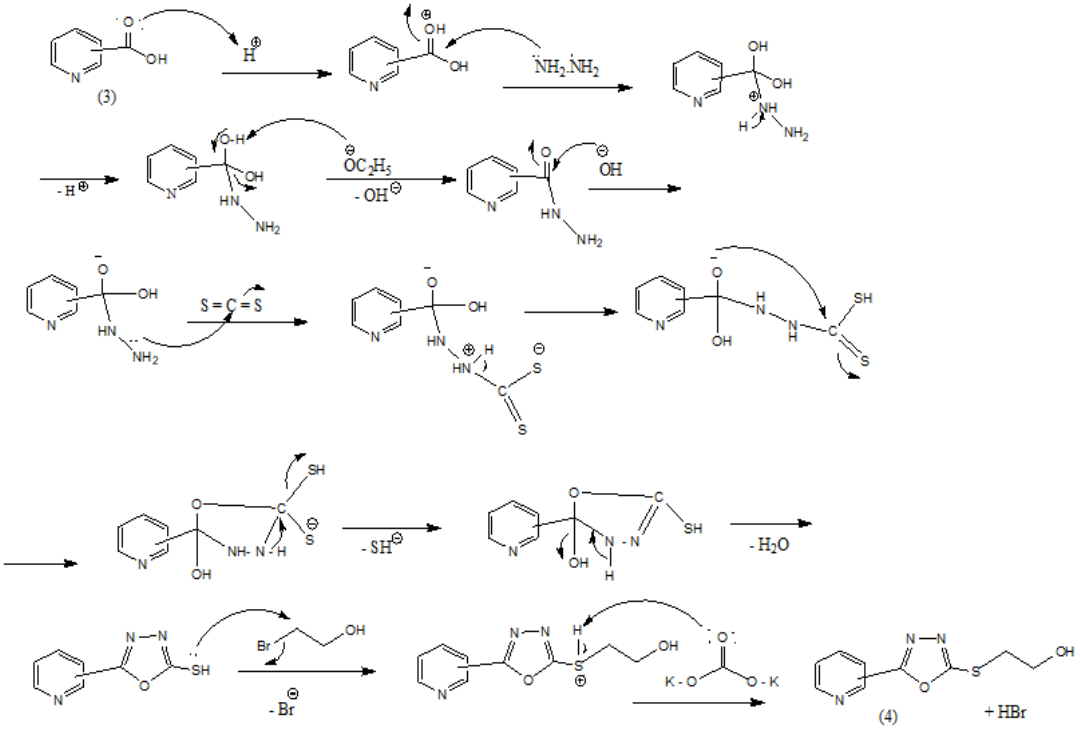

Figure 4: Suggested mechanism for the formation of 5-pyridyl-1, 3, 4-oxadiazole-2-thion derivatives.

Ɣ-lactones, an important group of oxygen heterocycles, display a broad range of biological properties including antibiotic, antifungal, antiviral, anti-inflammatory and many others. Common approaches adopted for the synthesis of Ɣ- lactone ring involve cyclisation by either C-C or C-O bond generation. The ring opening of epoxides with enolates, in the presence of a Lewis acid, is a useful method to generate Ɣ- lactones (5) in good yields (Figure 5) [50,51,52].

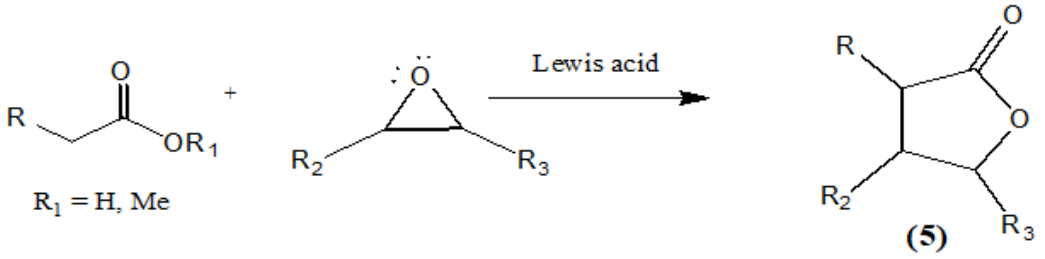

Figure 5: Ring opening of epoxides with esters or acids.

Probable mechanism developed for the formation of ɣ-lactone derivatives (5) can be rationalized as below Figure 6.

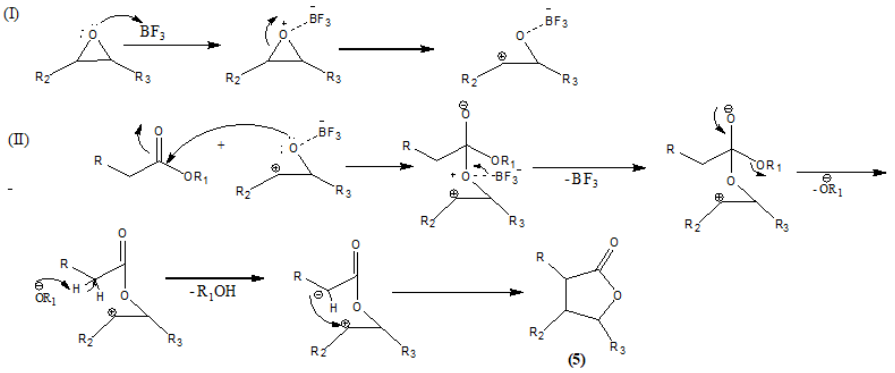

Figure 6: Mechanism developed for the formation of gama lactone derivatives (**5**).

In a mechanistically interesting reaction the carbonyl of a delta-alkenyl ketone traps the pi-complex obtained by treatment of the olefin with an electrophile, resulting the corresponding acetal (6). This unique approach to electrophile-induced cyclisations takes advantage of the nucleophilicity of carbonyl oxygen of the ketone (Figure 7).

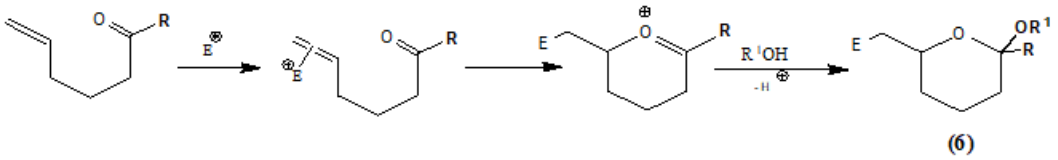

Figure 7: Synthesis of acetal derivative.

The most feasible mechanism proposed for the formation of acetal derivative (6) can be outlined as below Figure 8.

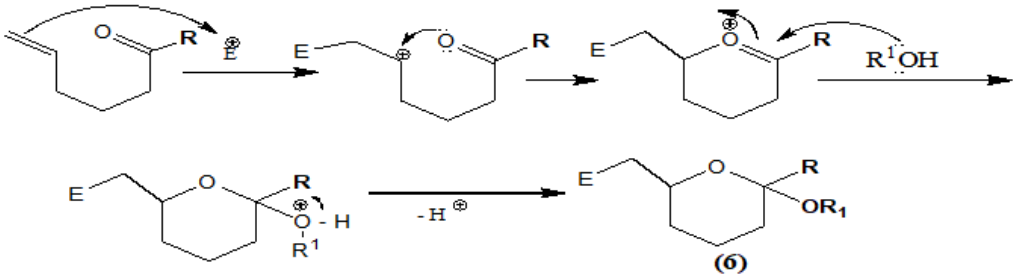

Figure 8: Mechanism proposed for the formation of acetal derivative.

NBS mediated cyclisations of two delta-alkenyl ketones, (7) and (8) have been employed to get the products (9) and (10) in high yields [53]- Figure 9.

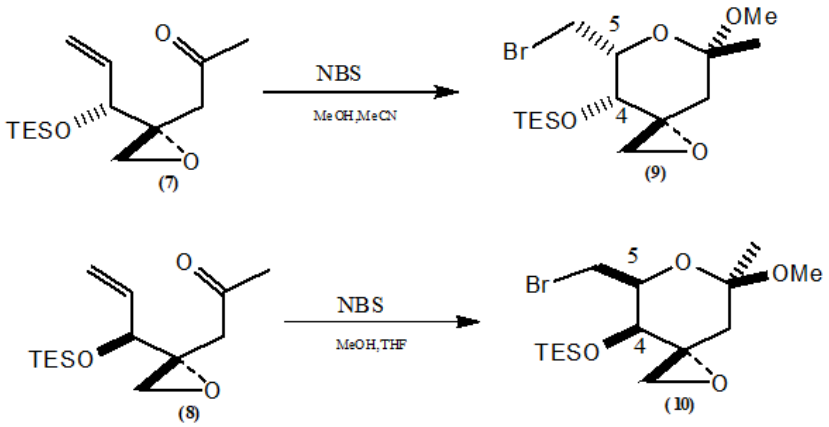

Figure 9: Synthesis of cyclization products.

Possible mechanism suggested for the formation of (9) can be rationalized as below Figure 10.

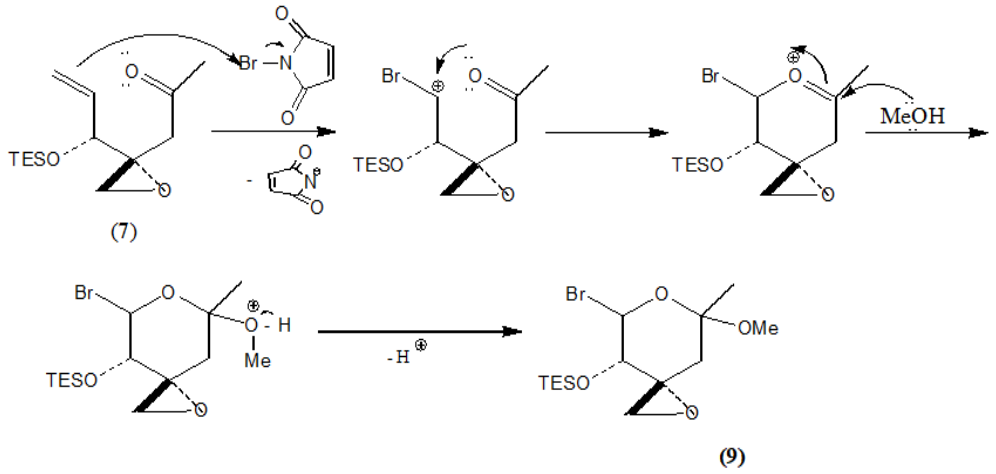

Figure 10: Suggested mechanism for the formation of cyclisation product.

Mechanism developed for the formation of cyclisation product (10) is analogous to that proposed for the compound (9). In a recent work bromo-lactonization of 3-allyl benzoic acid (11) has been achieved by N-bromo phthalimide(12) in presence of a chiral bifunctional sulphide catalyst to afford the compound (13) in excellent yields [54].

Literature discloses that the mechanism of formation for the compound (13) has not been suggested earlier; therefore, the possible mechanism proposed that proceeds via a free radical formation in presence of a chiral catalyst can be depicted as below Figure 11.

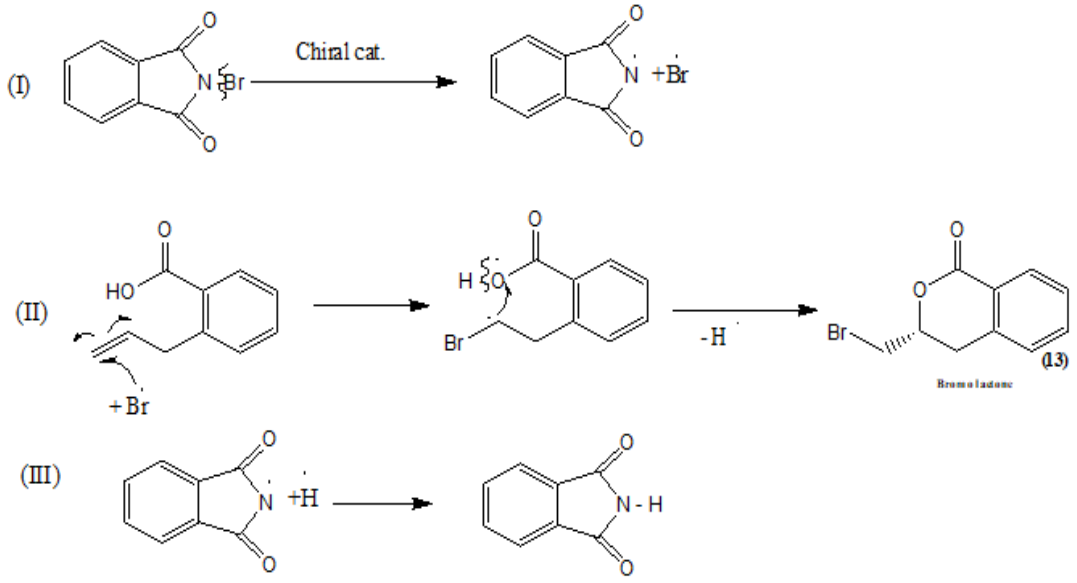

Figure 11: Radical mechanism developed for the formation of bromo-lactone.

The use of metal coordinated alcohols (14) as the nucleophilic source for the cyclization of pyran-like structures (15) has also been explored (Figure 12).

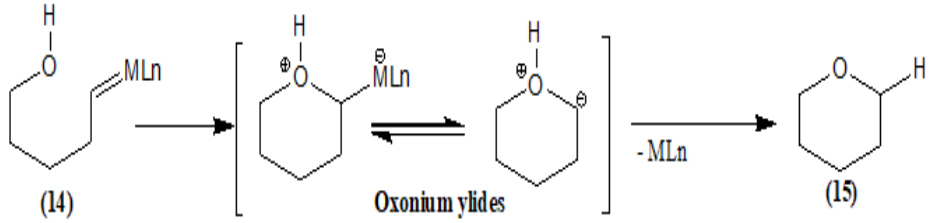

Figure 12: Synthesis of pyrans.

Possible mechanism proposed for the formation of pyran structure (15) can be discussed as below Figure 13.

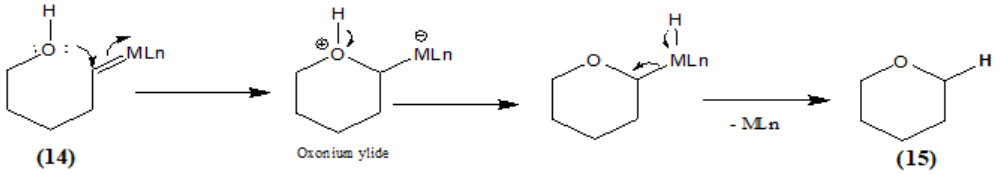

Figure 13: Mechanism developed for the formation of pyran like structure-(**15**).

Hydroxy alkenes (16) have been transformed to tetrahydropyrans of the type (17) in presence of mercuric acetate and bromine in THF. In this mercury (II)-mediated cyclisation both cis and trans products are obtained in high yields Figure 14.

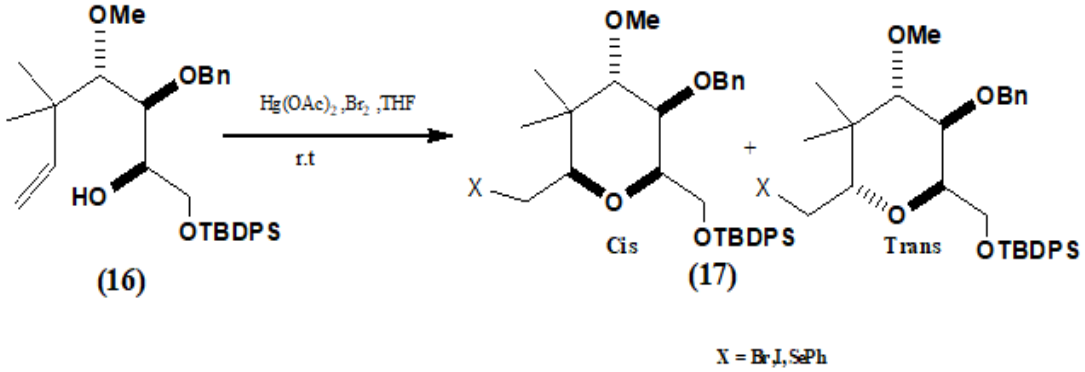

Figure 14: Synthesis of tetrahydropyrans of the type (**17**).

Plausible mechanism developed for the formation of tetrahydropyrans of the type (17) can be illustrated as below Figure 15.

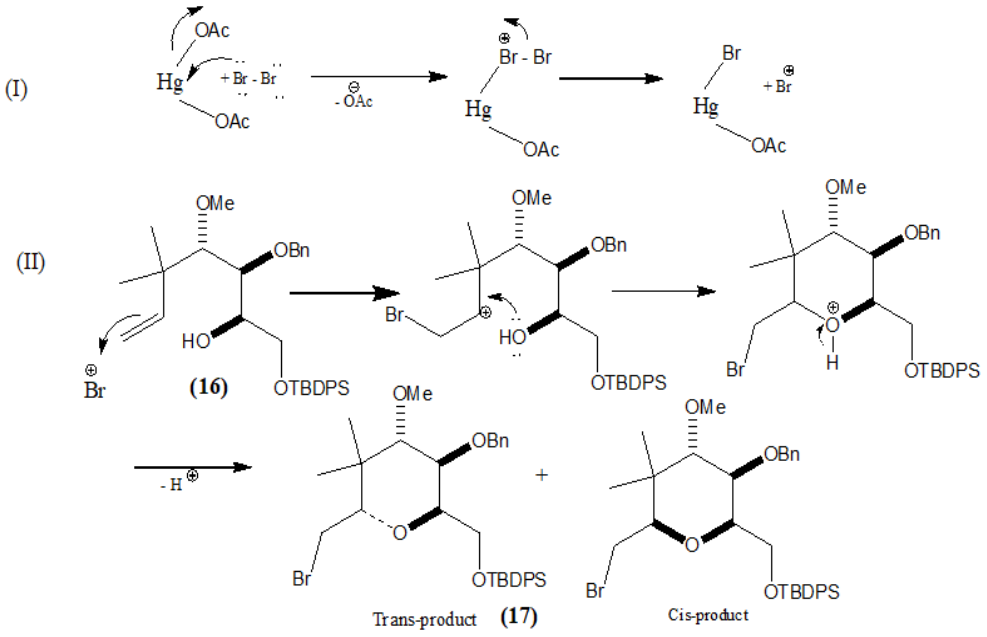

Figure 15: Proposed mechanism for the formation of tetrahydropyrans (**17**).

Applications

Oxadiazoles belong to group of heterocyclic compounds that have generated major interest in the field of medicinal chemistry. They are frequently occurring motifs in drug like molecules, and are often used with the intention of being bioisosteric replacements for ester and amide functionalities. 1,3,4-oxadiazole is widely investigated because of its significant interacting potential with various binding sites in the biological systems and has been reported to possess a series of pharmacological activities such as anticancer, antidiabetic, antimicrobial, antihypertensive, muscle relaxants, anticonvulsant, and anti-inflammatory agents. Some of the commercially available clinical drugs containing 1,3,4-oxadiazole nucleus are Furamizole(18),Tiodazosin (19) etc. 2-thione-1,3,4-oxadiazole derivatives have been found as potential anti-diabetic agents.

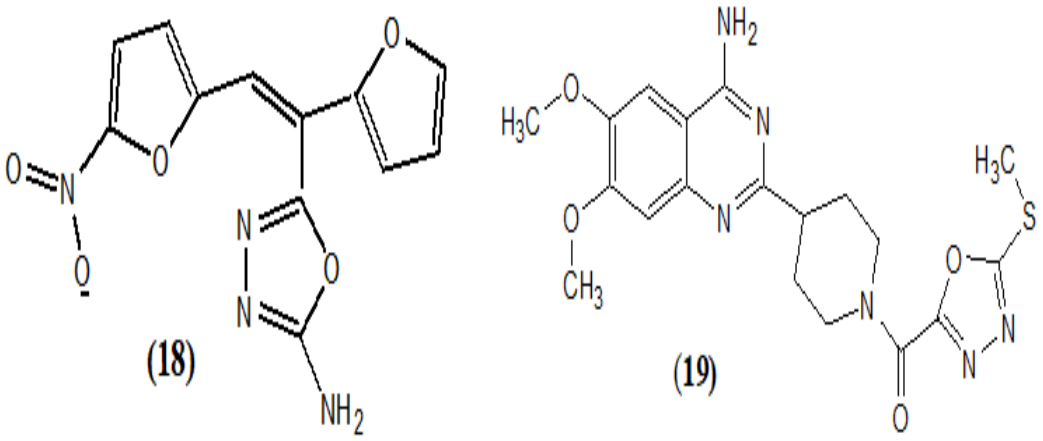

Figure 16: Structure of Furamizole (Anti-bacterial) and Tiodazosin (Anti-Hypertensive).

Due to the potential biological activity of these compounds, they are also used in agiculture as herbicides and insecticides. The compounds exhibiting insecticidal activity also include symmetrical 2,5-bis(2,4- dichlorophenyl)-1,3,4-oxadiazole derivatives (20). Such compounds show strong activity against house flies, flies and leaf rollers Figure 17.

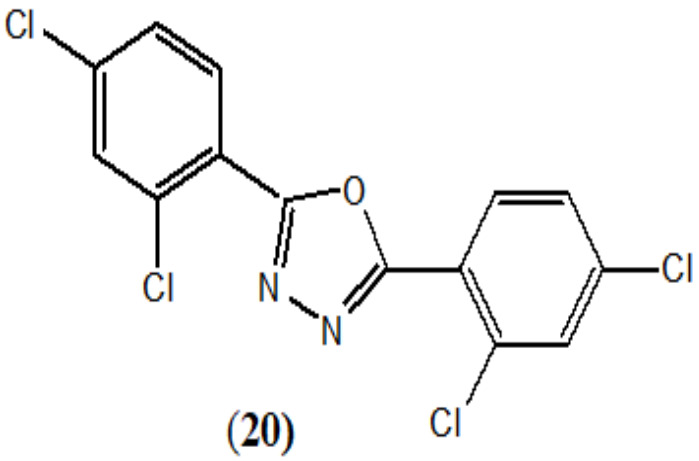

Figure 17: -2,5-bis(2,4- dichlorophenyl)-1,3,4-oxadiazole derivative (DCPO)(**20**).

An interesting compound with anticancer activity is Zibotentan (21). It is a specific ETA receptor antagonist used in the treatment of severe prostate tumors. Another example of medicinal importance used in cardiovascular diseases is Thiodiazosin (22). This compound includes a quinazoline structure and a 1,3,4-oxadiazole ring used to treat cardiovascular disease related to hypertension.

Six-membered oxygenated heterocycles are probably the most common structural motifs spread across natural products, from simple glucose to structurally complex metabolites such as leucascandrolide A and phorboxazole A and B. Lactones are cyclic esters of hydroxy carboxylic acids, containing a 1-oxacycloalkan-2-one structure, or analogs having unsaturation or heteroatoms replacing one or more carbon atoms of the ring.Ɣ-lactones are present in the structure of several natural products, such as the Ɣ-saturated butyrolactone and the α,β-unsaturated butenolides. Within the lactone family, sesquiterpenes are the most powerful antimicrobial agents for plants and animals. Some important examples of antimicrobial sesquiterpene lactones are damsin, cnicin, onopordopicrin, neoambrosin, ambrosin,and hymenin. Coumarins have been found to decrease tissue inflammation and edema and inhibit the biosynthesis of prostaglandins. Since prostaglandins are inflammatory mediators,so the combined effects are of great relevance . Helenalin is another outstanding anti-inflammatory compound. It is a bifunctional sesquiterpene lactone containing an α,β-unsaturated endocyclic ketone and an α-methylene Ɣ-lactone ring cis-fused to a carbocyclic skeleton. 7-Amino-4-methyl-2H-chromen-2-one, an amino coumarin has been found to posses significant cancer cell inhibitory activity. Spironolactone, the prominent steroidal compound is used as an important drug in the antihypertensive arsenal. This lactone is a potassium-sparing diuretic marketed under the name Aldosterone®. The macro-lactones amphotericin B and natamycin, marketed under the trade names of Fungizone® and Natacyn®, respectively, are antifungal drugs. The first macrocyclic lactones developed and used as ant-parasitic agents are avermectins (abamectin, ivermectin, eprinomectin, doramectin, and selamectin. 20(S)-Camptothecin , a natural product isolated from the Chinese tree Camptotheca acuminata, has a pentacyclic system formed by a quinoline moiety, a pyrrolidine ring, a lactam ring, and an α-hydroxy delta-lactone ring. Extracts of this plant are used in traditional Chinese medicine as a natural drug for cancer treatment.

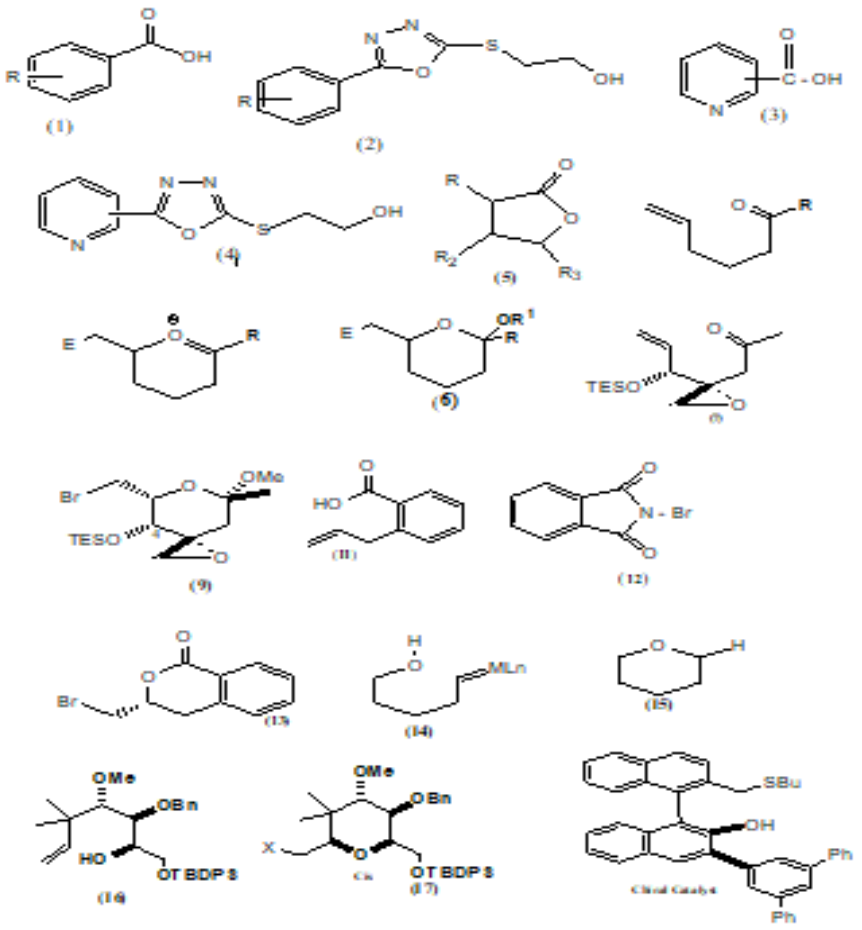

Figure 18: Structures Oxadiazoles and allied oxygen heterocycles.

CONCLUSION

In conclusion, we have developed innovative mechanisms for a wide range of oxadiazole derivatives, lactones and allied oxygen heterocycles and delineated some elegant synthetic methods for the construction of these compounds. Moreover, a broad spectrum of applications of pharmacological importance of these heterocycles have also been discussed.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest in this study.

DATA AVAILABILITY STATEMENT

Not applicable as it is purely a mechanism based article.

FUNDING

None declared.

DECLARATION

It is to certify that the mechanisms developed /suggested in this manuscript for a range of compounds are unknown and have not been published or submitted elsewhere in any other journal.

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