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Review Article

PROGRESS IN THE PATHWAYS FOR SYNTHESIS OF ISOXAZOLES SYNTHONS AND THEIR BIOLOGICAL ACTIVITIES

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ABSTRACT

Isoxazole and its derivatives are one of the very important classes of heterocyclic compounds which displaying a broad spectrum of biological activities which have made them very important structures in the field of medicinal chemistry. Isoxazoles are clinically proven to be very active as antibacterial, antifungal, anti-inflammatory, anticancer, anti-tubercular and antineoplastic agents. The different derivatives of isoxazole which exhibits differences in the structure have shown a vast diversity in their medicinal properties which have proven them as very beneficial in the progress of novel therapeutic agents which shows enhanced effectiveness and minor harmfulness. Hence, because of this widespread research on isoxazole from so many years, due to this reason, it has become necessary to analyse new progress in the synthetic routes and widespread range of biotic activity of isoxazole. With this conclusion, the present evaluation will be useful for the novel drug discovery of isoxazole molecules.

Keywords: Isoxazole, Antibacterial, Antifungal, Anti-inflammatory, Analgesic, Different synthetic methods.

1. INTRODUCTION

Heterocycles which having nitrogen along with them also having atoms such as oxygen and sulphur have gained considerable attention from pharmaceutical scientists as they show diversified biological activities. Such moieties having two or more active binding sites in a single molecule are used as synthons for the synthesis of a large number of heterocyclic compounds. Bioactive compounds are a worthwhile contribution to the field of heterocyclic chemistry [1]. Isoxazole shows various biological activities and similarly forms a very important part of several biodynamic agents [2]. The structure of Isoxazole (**1a**), its partial saturated analogues isoxazolines (**1b-d**) and its completely saturated analogue is known as the isoxazolidine (**1e**), shown in Fig. 1.

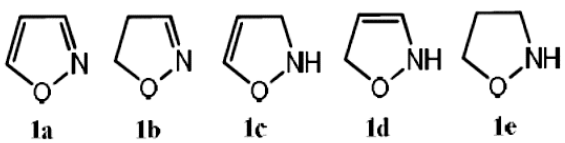

Fig. 1: Structure of Isoxazole and its Analog

The derivatives of Isoxazole playing a very important part in the organic chemistry branch. Because of their versatile biological importance, a significant amount of research effort has been focused on this molecule [3]. The isoxazole and its derivatives are also well-thought-out to be important synthons. Isoxazole and its analogues display different biological activities such as antibacterial, analgesic, antifungal, anti-inflammatory, etc. [4].

This review represents an overview of the preparation and biological activities of isoxazole and its derivatives. In the first part, we propose the outline of the general synthetic methods of isoxazole and its derivatives. The second part is about the information of different biological activities of isoxazoles and their derivatives.

2. DIFFERENT SYNTHETIC METHODS AND BIOLOGICAL ACTIVITIES OF ISOXAZOLE AND THEIR DERIVATIVES

There have been several practically important routes to synthesize isoxazoles, their derivatives and also their biological activities.

V. D. Joshi *et al.*, give the well-established method for the synthesis of substituted isoxazole from chalcones by using Claisen- Schmidt condensation of aldehyde, acetophenone and $NH_2OH.HCl$ is shown in Fig. 2 [5].

K.C. Gautam et al. synthesized the 4,5-dihydro-5 (substituted phenyl)-(3-thiophene-2-yl)isoxazole from 2-acetyl thiophene and substituted aldehydes as shown in Fig. 3. The newly synthesized derivatives show antimicrobial activity [6].

V. Tirlapur *et al.,* gave the reaction of 5-Bromo-2-acetyl Benzofuran with different aromatic aldehydes in presence of alkali that gives chalcones which on further reaction with hydroxylamine hydrochloride formed Isoxazole derivatives having Benzofuran as shown in Fig. 4 [7].

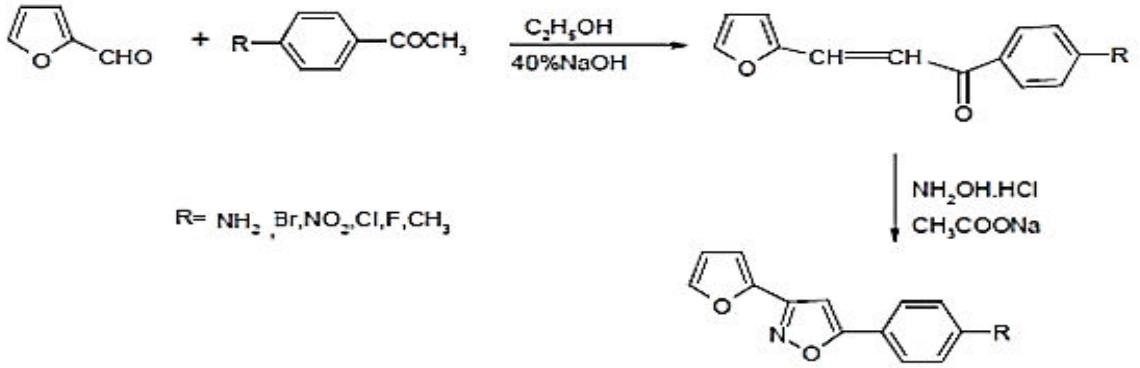

Fig. 2: Synthesis of isoxazole derivative from furfuraldehyde

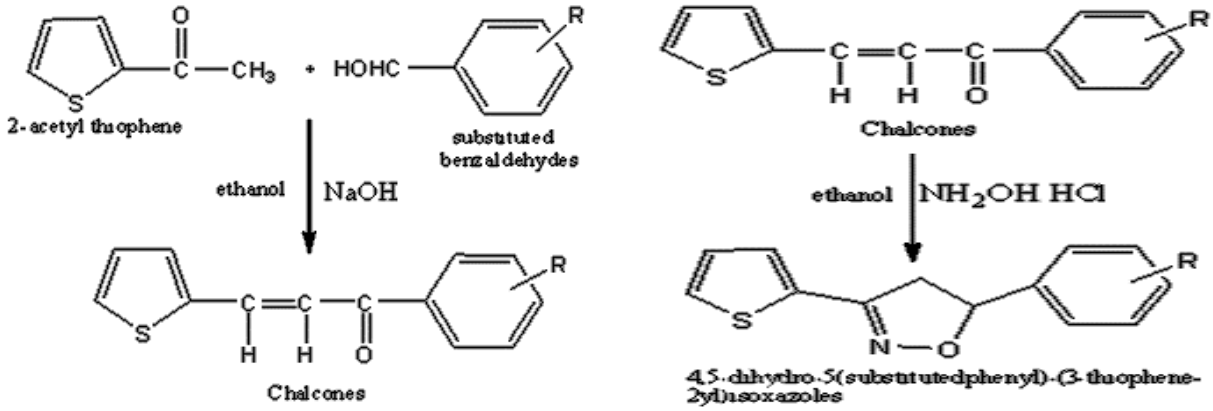

Fig. 3: Synthesis of isoxazole derivative from 2-Acetyl Thiophene

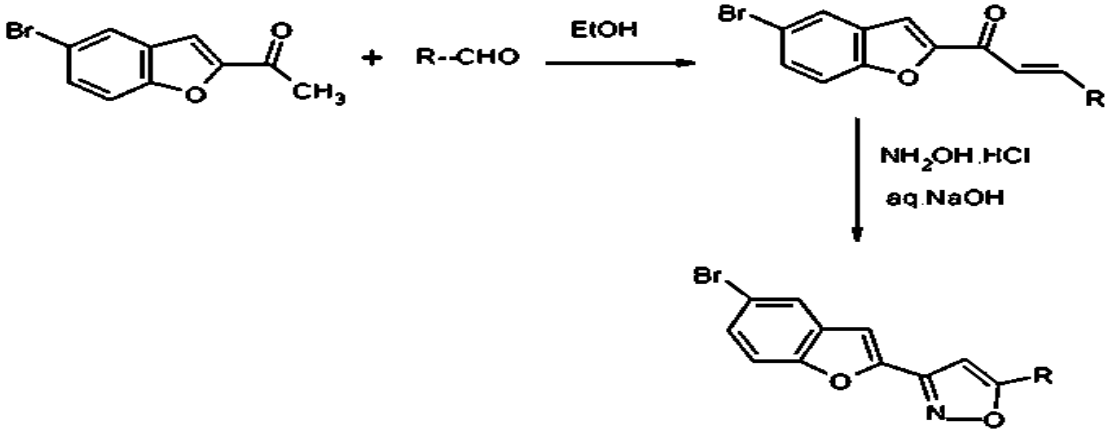

Fig. 4: The synthesis of isoxazole derivatives from benzofuran

P. D. Jagadeesh and co-authors, have prepared a class of isoxazole derivatives. The derivatives were obtained by the reaction of 4-Methylthiobenzaldehyde which get reacted with numerous aryl ketones in the presence of potassium hydroxide afford a series of chalcones i. e. 1-aryl-3-(4-methylthiophenyl)-2-propene-1-ones as depicted in Fig. 5. Chalcones undergo a bromination reaction with bromine in the presence of chloroform to get dibromo-propanones, which they later treated with hydroxyl-amine hydrochloride in presence of aqueous alkali to get 3, 5-diaryl-lisoxazoles. A few of the newly synthesized derivatives of isoxazole displayed hopeful antimicrobic activities [8].

A. Sharma *et al.,* synthesized a series of 3-propene-1,2-benz-isoxazole derivatives as shown in Fig. 6. The newly synthesized isoxazole derivatives show good to moderate antimicrobial activity [9].

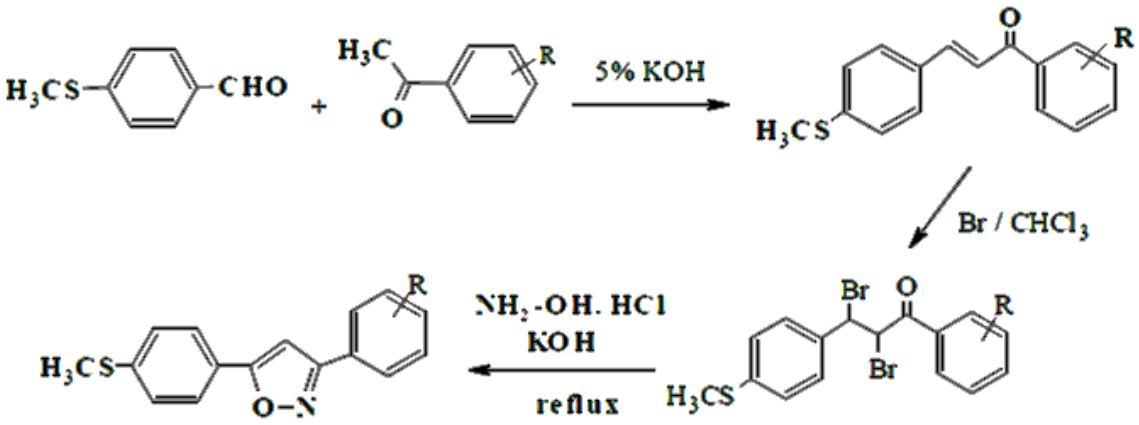

Fig. 5: The synthesis of isoxazole derivatives

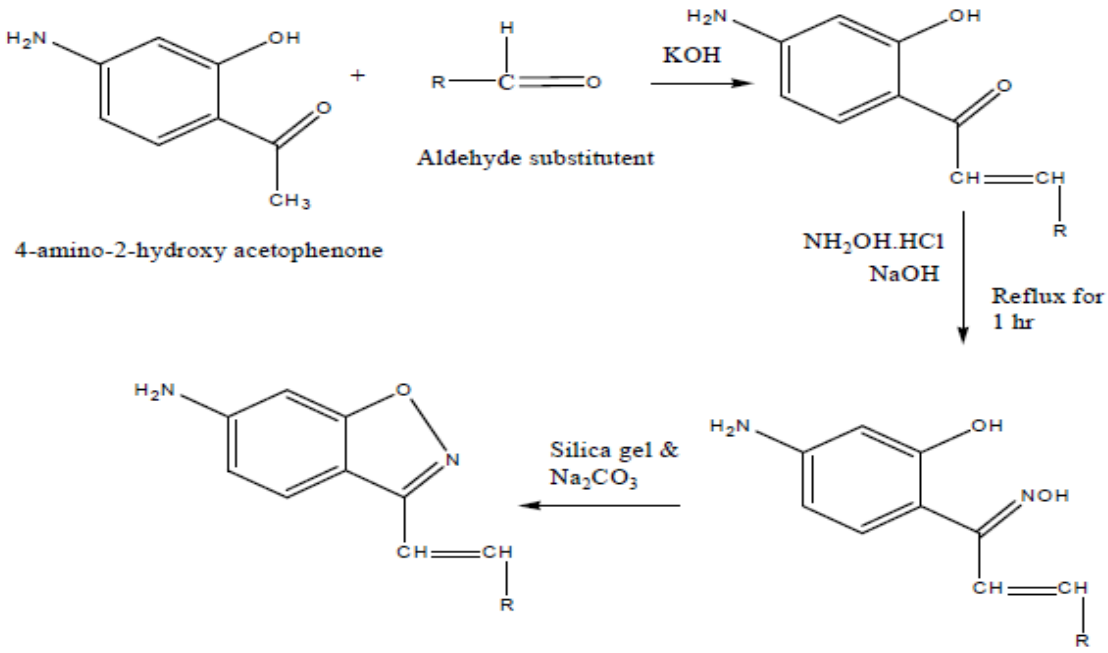

Fig. 6: The synthesis of 3-propene 1,2-benzisoxazole derivatives

R. Kataria *et al.,* have been reported the synthesis of substituted diphenyl isoxazoles. Various substituted aromatic aldehydes when reacted with aromatic ketones in the presence of sodium hydroxide (NaOH) yield chalcones which further undergo reaction with bromine in presence of glacial acetic acid yielded chalcone

dibromide. This further undergoes the subsequent cyclization reaction with the compound hydroxylamine hydrochloride in the presence of triethylamine (TEA) affording substituted diphenyl isoxazoles with a good yield as shown in Fig. 7. The prepared novel derivatives of isoxazole were screened for their anti-inflammatory activity [10].

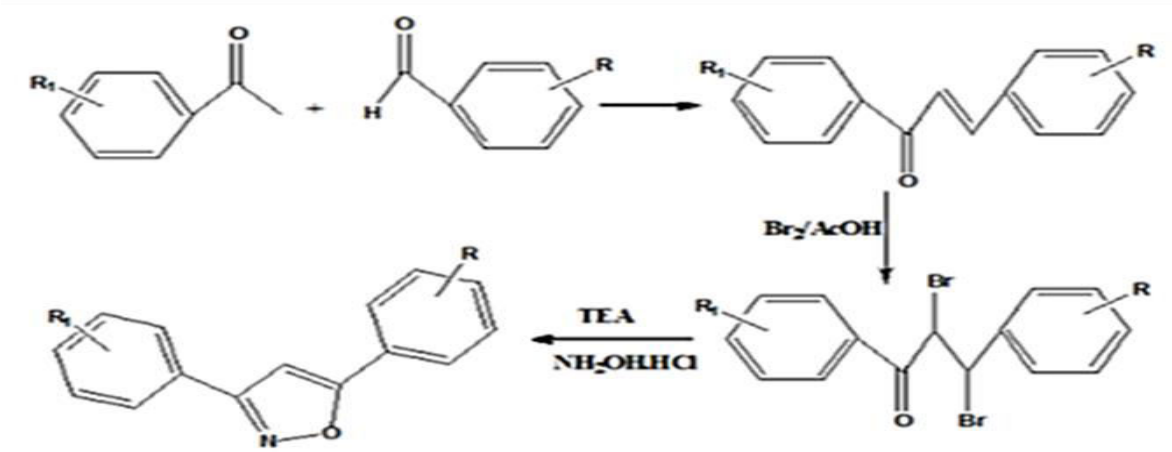

Fig. 7: Synthesis of substituted diphenyl isoxazoles

K. Madhavi and co-authors, had conveyed the preparation of a series of 3-methyl-4nitro-5-(substitutedstyryl) isoxazoles as shown in Fig. 8. The newly synthesized derivatives with sterically hindered phenolic groups show good anti-inflammatory activity and also better antioxidant properties [11].

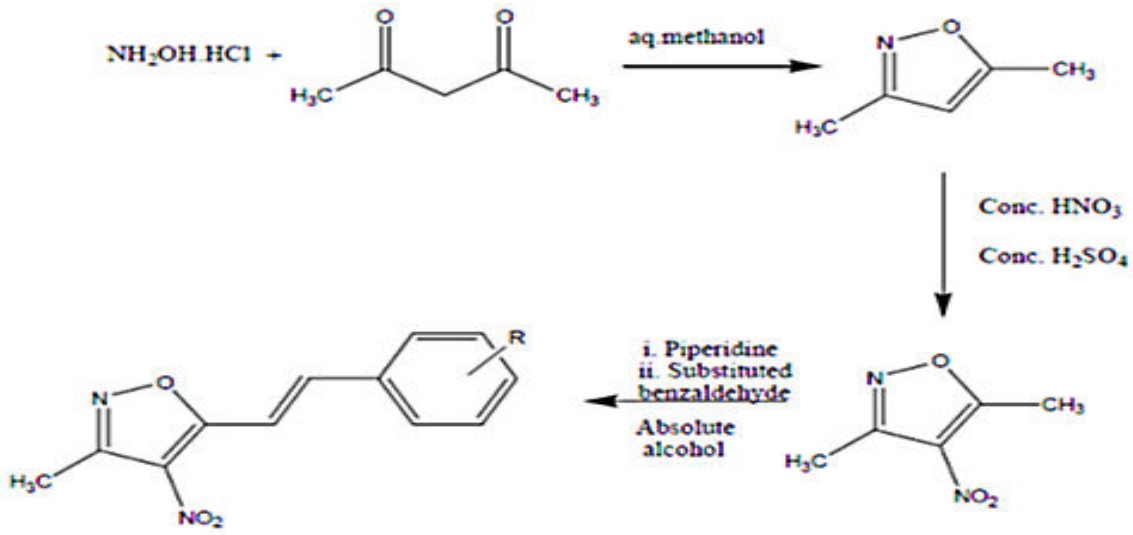

Fig. 8: Synthesis of 3-methyl-4nitro-5-(substituted-styryl) isoxazoles

Dou G. and co-authors, conveyed the preparation of a series of 5-aryl-isoxazole analogue synthesized by carrying out the reaction of 3-(dimethyl-amino)-1-arylprop-2-en-1-ones and hydroxylamine hydrochloride in the presence of an aqueous medium without using any catalyst (Fig. 9). This process is a green chemical process that exhibits several advantages such as ease carried out, minor reaction circumstances, high amount of product, and an environmentally kind method [12].

R. Khobare *et al.,* synthesized different isoxazole derivatives with the help of ultrasound methodology by the reaction of substituted aldehydes and acetophenones in the triethylamine and ethanol as shown in Fig. 10 [13].

S. B. Kasar *et al.,* have reported a green synthetic route using the ultrasound method for the synthesis of 4H-isoxazol-5-ones using itaconic acid as an organo-catalyst (Fig. 11) [14].

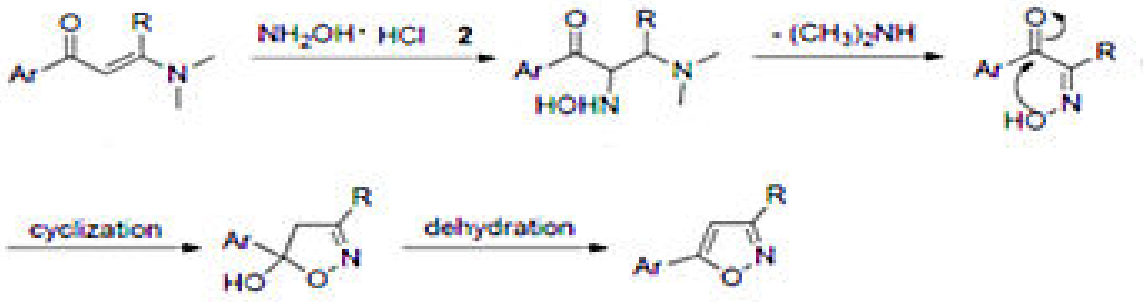

Fig. 9: The synthesis of 5-arylisoxazole derivatives

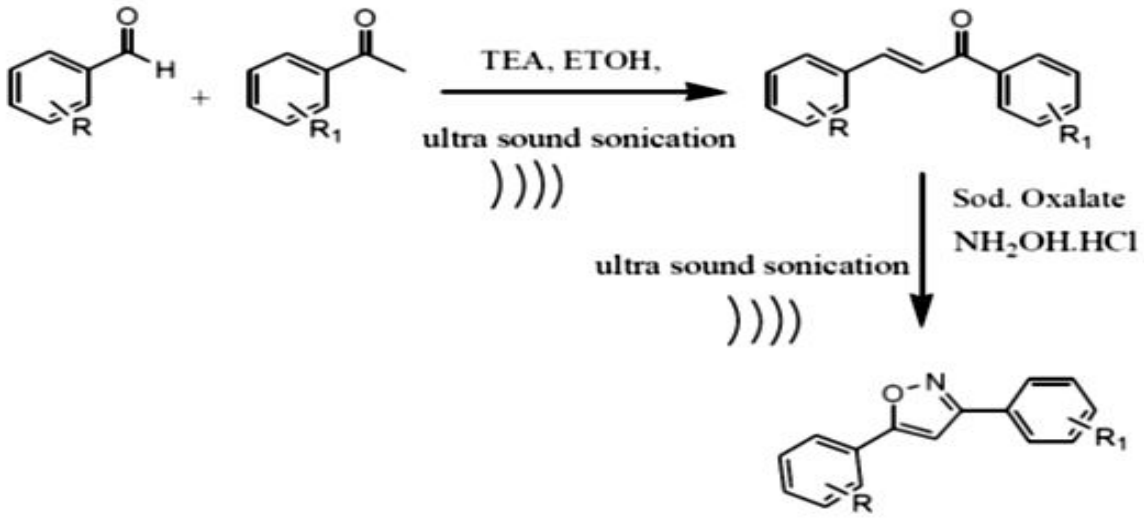

Fig. 10: Green route for the preparation of substituted isoxazole analogue

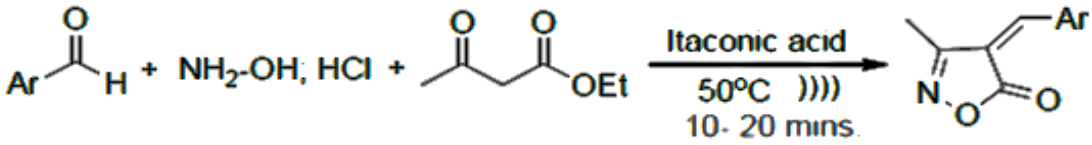

Fig. 11: Preparation of 4H-isoxazol-5-ones by ultrasonic method

R. Y. Jin *et al.,* have reported the series of isoxazole derivatives which was synthesized by substituted chalcones and 2-chloro-6-fluorobenzene formaldehyde oxime with 1,3-dipolar cycloaddition (Fig. 12). The newly synthesized compounds were screened for antifungal activity against Pythium solani, Gibberella nicotiancola, Fusarium oxysporium f.sp. niveum and Gibberella saubinetii [15].

M. Brahmayya *et al.,* have reported the preparation of novel 5-aryl-4-methyl-3yl(imidazolidin-1yl methyl, 2-ylidene nitro imine) isoxazoles (Fig. 13). The preparation of biologically active 5-aryl-4-methyl-3yl-(Imidazolidin-1yl methyl, 2-ylidene nitro imine) isoxazoles is synthesized from 1-phenyl-propan-1-one. These newly synthesized compounds were tested for antifungal activities. These compounds exhibit good anti-fungicidal activity. These compounds shall be exploited further for the fungicidal activity to attain a potential pharmacophore [16].

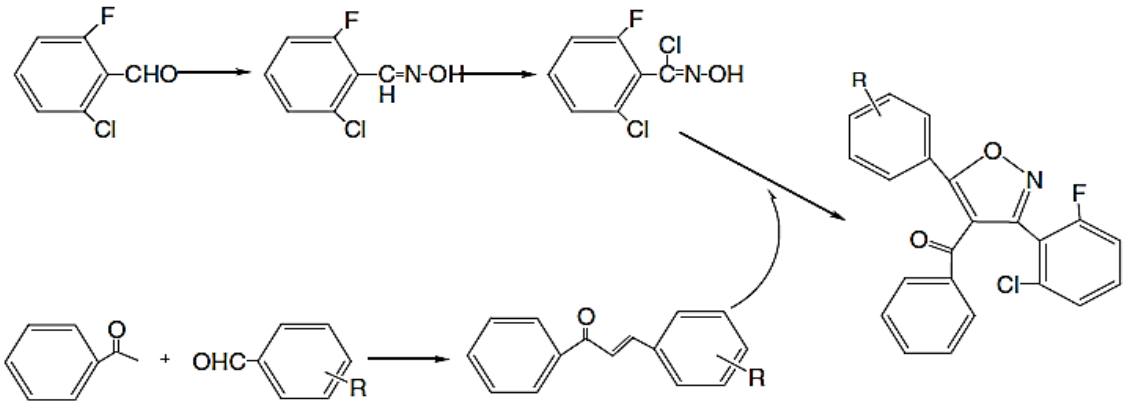

Fig. 12: Preparation of isoxazole derivatives

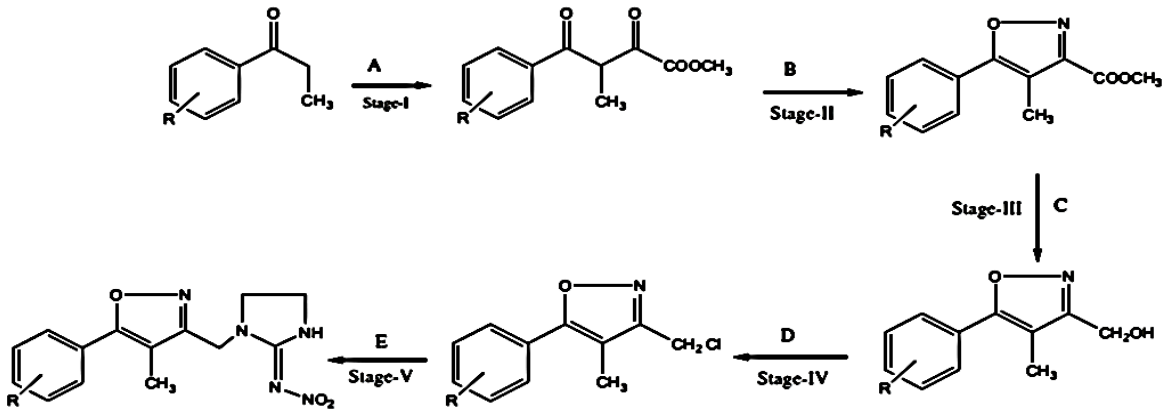

Fig. 13: Synthesis of of novel 5-aryl-4-methyl-3yl (imidazolidin-1yl methyl, 2-ylidene nitro imine) isoxazoles

3. CONCLUSION

Isoxazoles are compounds that are easily available and they show very high chemical reactivity. Such a class of heterocycles contains a five-membered system of a ring consisting of three carbon atoms along with the first position of oxygen and the second position of the nitrogen atom. Evolving research attention on the isoxazole moiety and its derivatives previously has been proven by the different research groups. The interest associated with these molecule isoxazoles and their derivatives is based on their versatility as one of the synthetic building blocks. This review article gives detail information on different synthetic methods and biological activities of isoxazole and its analogues. Hence, this review article may useful for medicinal chemists and also help in the development of new medicinal drugs.

4. ACKNOWLEDGEMENT

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Conflict of interest

In this review paper, there are no conflicts of interest among the authors.

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