JCRS

Journal of Chemical Reactivity and Synthesis 2023: 13(3) 202-221

Research Article

Synthesis Mechanism of formation and Advanced applications of some unique five membered heterocycle derivatives

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ARTICLE INFO:

Received:
5 July 2023

Accepted:
10 September 2023

Available online:
18 September 2023

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ABSTRACT

Heterocyclic compounds are widely distributed in nature and have played a vital role in synthetic organic chemistry. Five membered heterocycles, an important class of heterocyclic compounds, have been frequently synthesized and find a diverse range of applications in chemistry, biology and biochemistry of both pharmacological and chemical importance. Palladium-catalyzed cyclisation of different enynethiols has afforded a series of substituted thiophenes. The substrates, (Z)-2-en-4-yne-1- thiols, undergo cyclo isomerisation in dimethyl acetamide in the presence of catalytic amounts of PdI_2 along with KI, to yield corresponding thiophenes **4**. Chiral imidazoles have been synthesized by thio-Ugi reaction. The method involves the treatment of thioamides with ammonia and cyclisation of the resulting substituted amidines in aqueous hydrochloric acid to afford corresponding imidazoles **11**.

This article will discuss on various synthetic pathways adopted for the synthesis of different five membered heterocycle derivatives and explore the mechanistic aspects apart from the recent applications of some unique compounds.

Keywords: Thiazole, Imidazole, Furan, Synthesis, Oxadiazole, Thioamides.

1. Introduction

Heterocyclic compounds are a unique class of compounds that have a wide range of physical, chemical, and biological properties. They are present in pharmaceuticals, agrochemicals, dyes, and many others. In addition to naturally occurring compounds, many synthetic heterocyclic compounds with several physiological and pharmacological properties are also known. Five-membered heterocycles are among the broadest class of organic compounds. Major compounds of this class are imidazole, isoxazole, pyrazole, oxazole, diazole, thiazole, triazole, and other aliphatic heterocycles .These serve as cornerstones of several drugs and bioactive compounds. Isoxazole, imidazole, and thiazole moieties are ubiquitous as natural products. Pyrrole and pyridine are the most important and well known nitrogen containing heterocycles of synthetic utility [1-4]. Thermolysis of triazolines (1a;NR2= morpholino) , yields a mixture of elimination products and the thiophene [5]. The synthesis of tri-substituted furans in quantitative yields by cyclisation of 3-alkyne-1,2-diols under heterogeneous catalysis has been demonstrated [6]. 3H indole gets converted to the indole by intermolecular thermal rearrangement [7]. Oxadiazole nucleus is one of the most important pharmacological scaffolds [8-12]. A common synthetic method involves the cyclisation of 1-acyl-4-alkyl/aryl semicarbazides/thio semicarbazides to 2-alkyl/arylamino-5-alkyl/aryl-1,3,4-oxadiazoles using special reagents and reaction conditions [13].

The aim of this work is to highlight a series of mechanisms suggested /proposed for different five membered hetero atom compounds. Although the compounds are known but the mechanisms were not discussed or developed earlier as revealed by the exhaustive literature survey. Apart from this, a range of recent and advanced applications of various heterocycles have also been outlined in this manuscript.

2. Discussion

Heterocyclic compounds are the most important of the traditional organic divisions of organic chemistry and can be found naturally in nucleic acids, hormones, vitamins, antibiotics and other substances.

Five-membered heterocycles, an important class of heterocyclic compounds, performed significantly in synthetic organic chemistry and enormous number of natural products. Synthesis and mechanism of formation of some important derivatives of five membered heterocycles having one or more than one hetero atom will be discussed under varying reaction conditions using versatile reagents and substrates.

2.1. Furans and Tetrahydrofurans

A number of methods for the synthesis of different substituted tetrahydrofurans have been described under varying reaction conditions [14]. An efficient stereo selective cyclisation method has been established for the synthesis of methylene tetrahydrofurans **1** from propargyl alcohols using Lewis acid catalysis [15]. $SnCl_4$ resulted the *E* isomer whereas ZnX_2, $InCl_3$, $FeCl_3$ and $AlCl_3$ yielded the *Z*-isomer (Scheme 1).

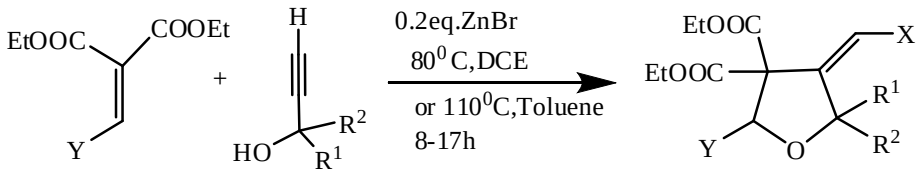


Figure-1

Y=COOEt,COPh,X=COOMe,SiR_3,R^1,R^2,=H,alkyl,Ph

Scheme 1. A stereoselective synthesis of methylenetetrahydrofurans (1).

Using Sharpless asymmetric epoxidation, highly-functionalized, enantiomerically pure THF derivatives **2** have been synthesized [16] (Scheme 2).

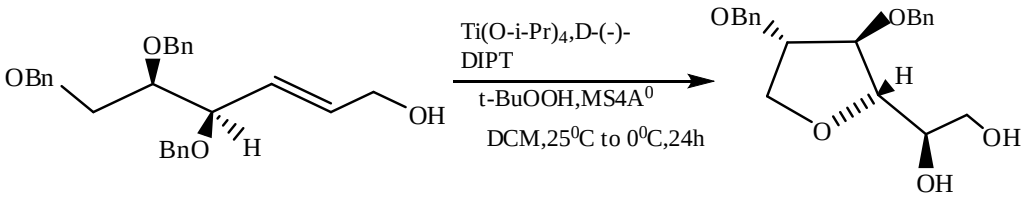


Figure-2

Scheme 2. Sharpless asymmetric epoxidation to enantiomerically pure THFs.

Under diverse reaction conditions using versatile reagents and substrates different methods for the synthesis of furans have also been reported [17-20]. Synthesis of polysubstituted furans has been demonstrated either from 1,4-dihydropyridines [21] or by palladium catalyzed coupling of butatrienyl carbinols with aryl halides and triflates [22]. Palladium catalysed allylated furans **3** from appropriate epoxypropargyl esters have also been synthesized [23] (Scheme 3).

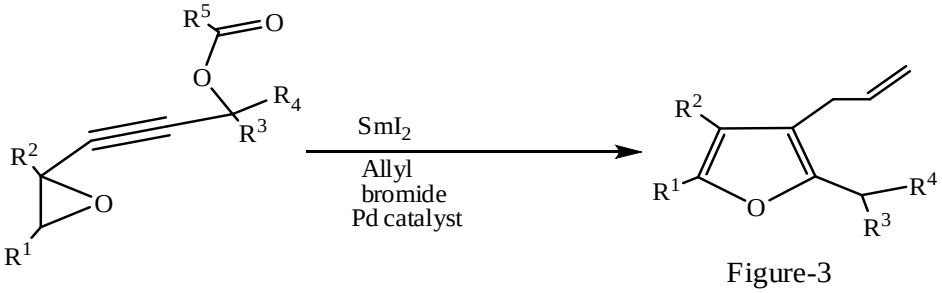


Figure-3

Scheme 3. Palladium-catalyzed synthesis of allylated furans.

2.2. Thiophenes

Palladium-catalyzed cyclisation of different enynethiols has afforded a series of substituted thiophenes. The substrates, (Z)-2-en-4-yne-1- thiols, undergo cyclo isomerisation in dimethyl acetamide in the presence of catalytic amounts of PdI_2 along with KI, to yield corresponding thiophenes **4** [24] (Scheme 4).

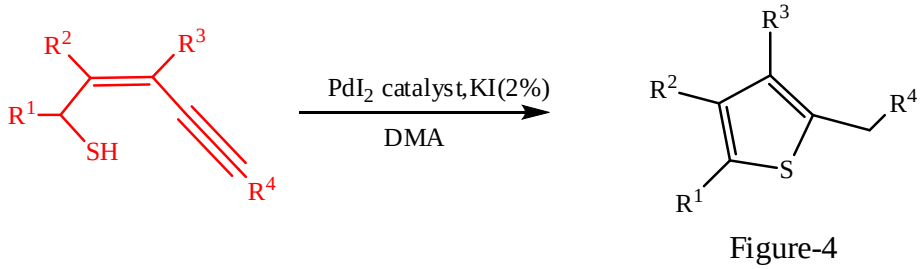
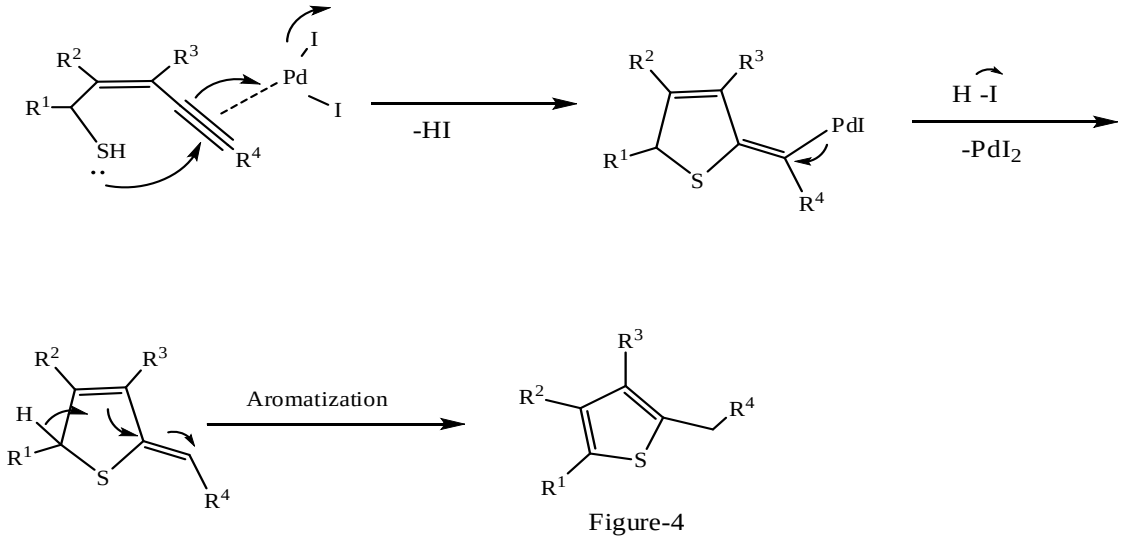


Figure 4. Cyclisation of enynethiols to thiophenes Mechanistically the formation of 4 can be rationalized. as – Scheme-4.



Scheme 4. Mechanism suggested for the formation of thiophene **(4)**.

1,3-Dicarbonyl compounds have been used in the synthesis of a wide range of tetra substituted thiophenes in a one-pot method [25]. An unusual synthesis of 2,3-diylthiophenes has also been reported [26].

2.3. Pyrroles

Pyrrole, a nitrogen heterocycle, exhibits a variety of applications in the field of medicines, polymers, and bioscience. Aside the earliest methods for the synthesis of pyrroles by Paal, Knorr, and Hantzsch, a modified method for Paal-Knorr synthesis of pyrroles **5**

using 1,4-dicarbonyl systems, obtained by the ozonolysis of allylated -ketoesters, has been reported [27].

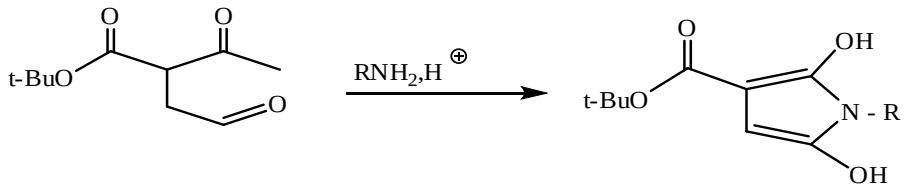


Figure-5

Probable mechanism developed for the modified Pall-Knorr synthesis of pyrrole derivative **5** can be depicted as below (Scheme 5).

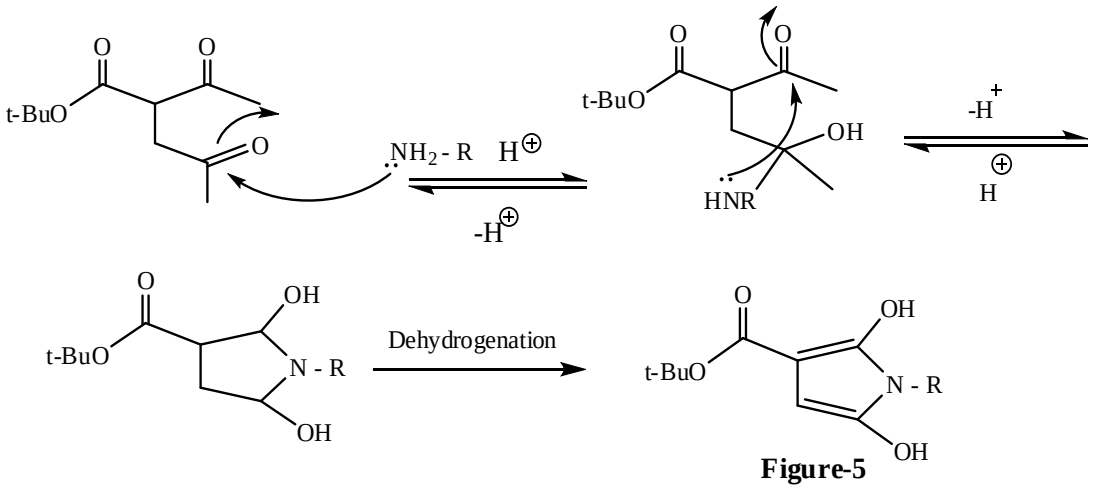


Figure-5

Scheme 5. Mechanism developed for the modified Pall-Knorr synthesis of pyrrole derivative (5).

Microwave assisted cyclocondensation of 1,4-dicarbonyl compounds using magnesium nitride as a source of ammonia, resulting in the synthesis of 2,5-disubstituted pyrroles **6** has also been reported recently [28] (Scheme-6).

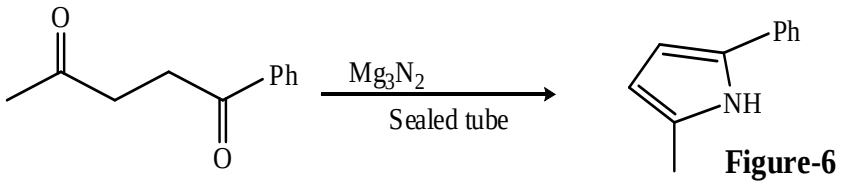


Figure-6

Scheme 6. Mechanism developed for the modified Pall-Knorr synthesis of pyrrole derivative (5).

1,2,3,5-Tetrasubstituted pyrroles **7** can also obtained in a chemoselective manner from primary amines and 1,3-diketones in two to three steps [29]. (Scheme 7)

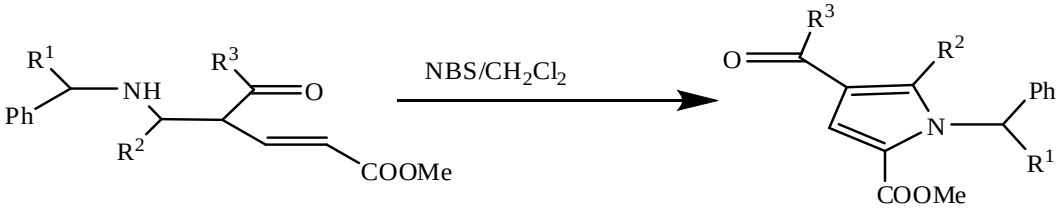


Figure-7

Scheme 7. Bromo-cyclisation to tetra substituted pyrroles (7).

2.4. Thiazoles

An important method for the synthesis of 2,4-disubstitued thiazoles **8** in excellent yields from alpha- bromo ketone and a thioamide or thiourea in an environment friendly ionic liquid at ambient reaction conditions has been recently reported [30].

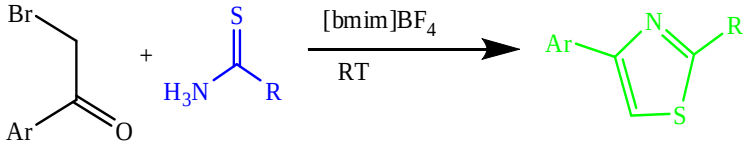


Figure-8

Plausible mechanism proposed for the formation of thiazole **8** can be rationalised as below (Scheme 8).

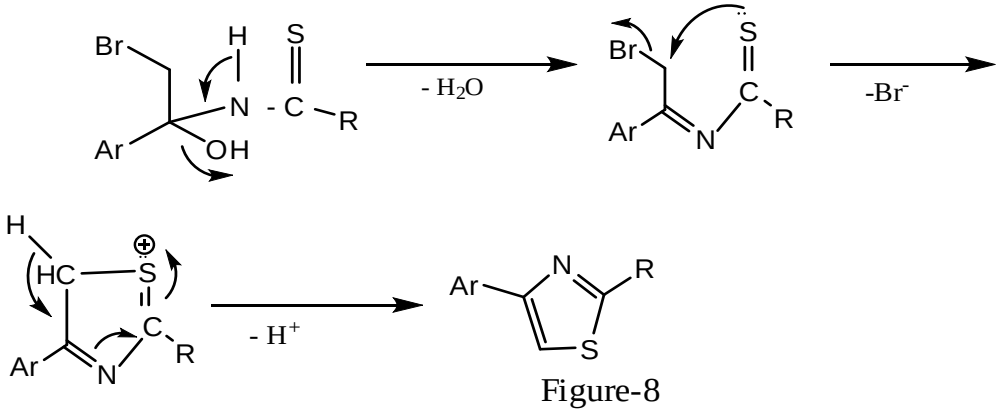


Figure-8

Scheme 8. Proposed mechanism for the Synthesis of thiazoles (8).

2,5-disubstitued and 2,4,5-trisubstitued thiazoles **9** can also be synthesized by intramolecular thia-Michael strategy [31] .The method is useful for introducing various C-, O-, or S- substituents at position- 2 of the thiazole ring (Scheme 9).

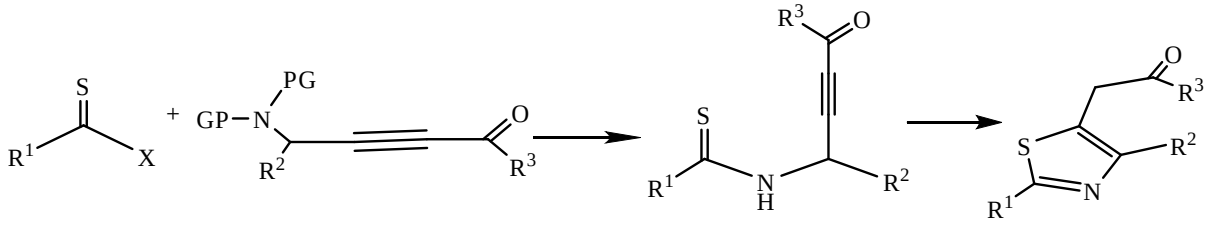


Figure-9

Scheme 9. Intramolecular thia-Michael reaction for the synthesis of substituted thiazoles.

2.5. Imidazoles

New methodologies have been developed for the synthesis of a wide range of imidazoles of significant medicinal importance Palladium-catalyzed cyclisation of o-pentafluorobenzoyl amidoximes has been reported to afford 1-benzyl-4-methylimidazoles **10** with different substituent variation at C_2-position [32] (Scheme 10).

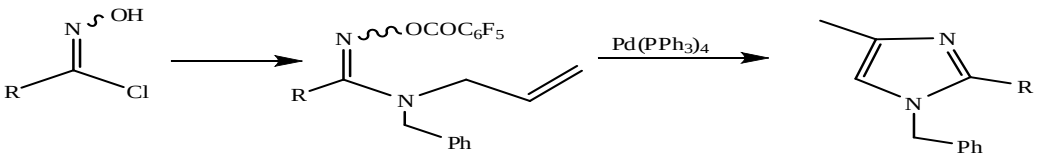


Figure-10

Scheme 10. Synthesis of imidazoles.

Chiral imidazoles have been synthesized by thio-Ugi reaction [33]. The method involves the treatment of thioamides with ammonia and cyclisation of the resulting substituted amidines in aqueous hydrochloric acid to afford corresponding imidazoles **11**.

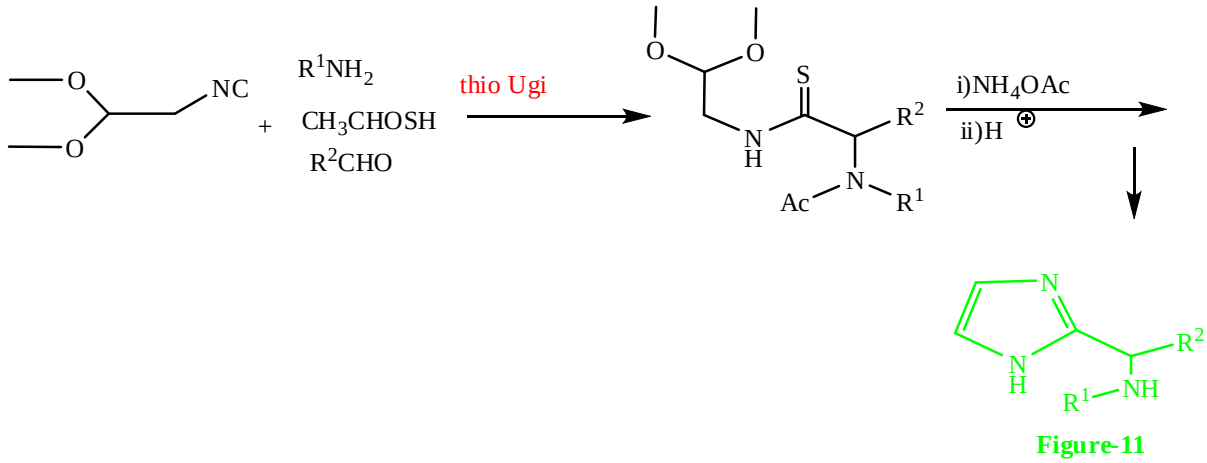
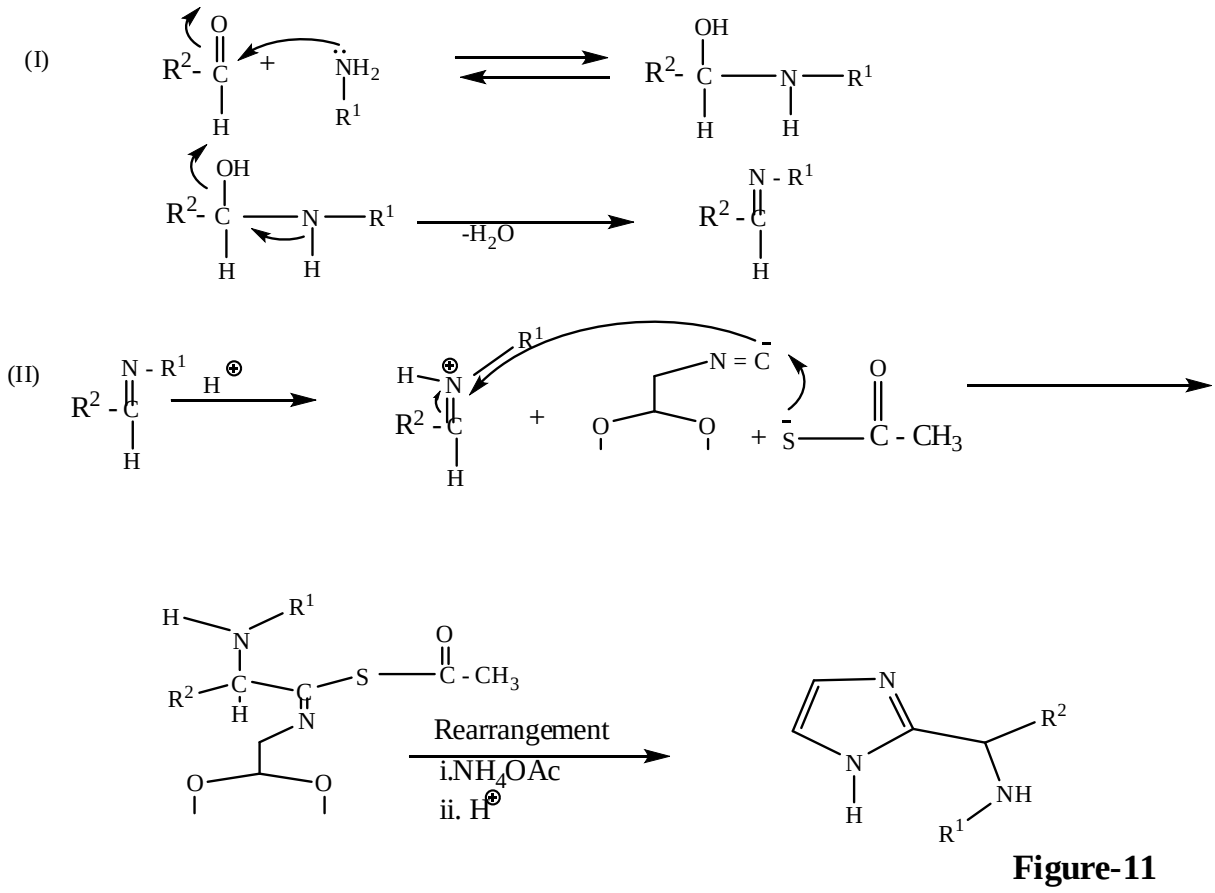


Figure-11

Since the mechanism was not developed earlier, therefore the probable mechanism proposed for the formation of corresponding imidazoles **11** can be discussed as (Scheme 11)

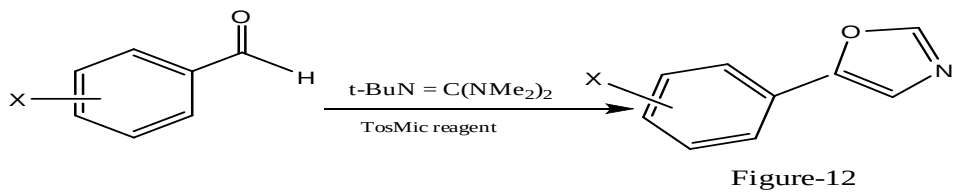
Synthesis of imidazole-2-thiones by nucleophilic substitution reaction of vinylic bormides with thioamides or thioureas has been recently reported [34]. 1,3,4-trisubstituted imidazole-2-thiones can easily be synthesised by this method. Alcohols and phenols may also be converted to the corresponding imidazoles by reaction with carbonyl diimidazole or carbonyl ditriazole in acetonitrile [35].



Scheme 11. Suggested mechanism for the formation of imidazole (**11**).

2.6. Oxazoles and Isoxazoles

A one-pot synthesis of 2,5-disubstituted oxazoles from benzyl halides and acyl chlorides involving an *in situ* formation of isocyanides has been reported [36] . The TosMIC [37, 38] and ROMPgel (ring opening metathesis polymers) TosMIC reagents have also been applied in the conversion of aldehydes to oxazoles **12** in good yields [39].



Scheme 12. Oxazole formation using TosMIC reagents.

Recently an environment friendly one-pot synthesis of 3,5-disubstituted isoxazoles **13** has been achieved from beta-diketones in an ionic liquid [40]. Plausible mechanism developed for the formation of **13** can be depicted as (Scheme 13).

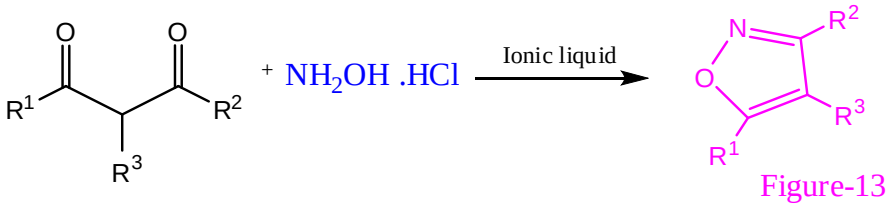
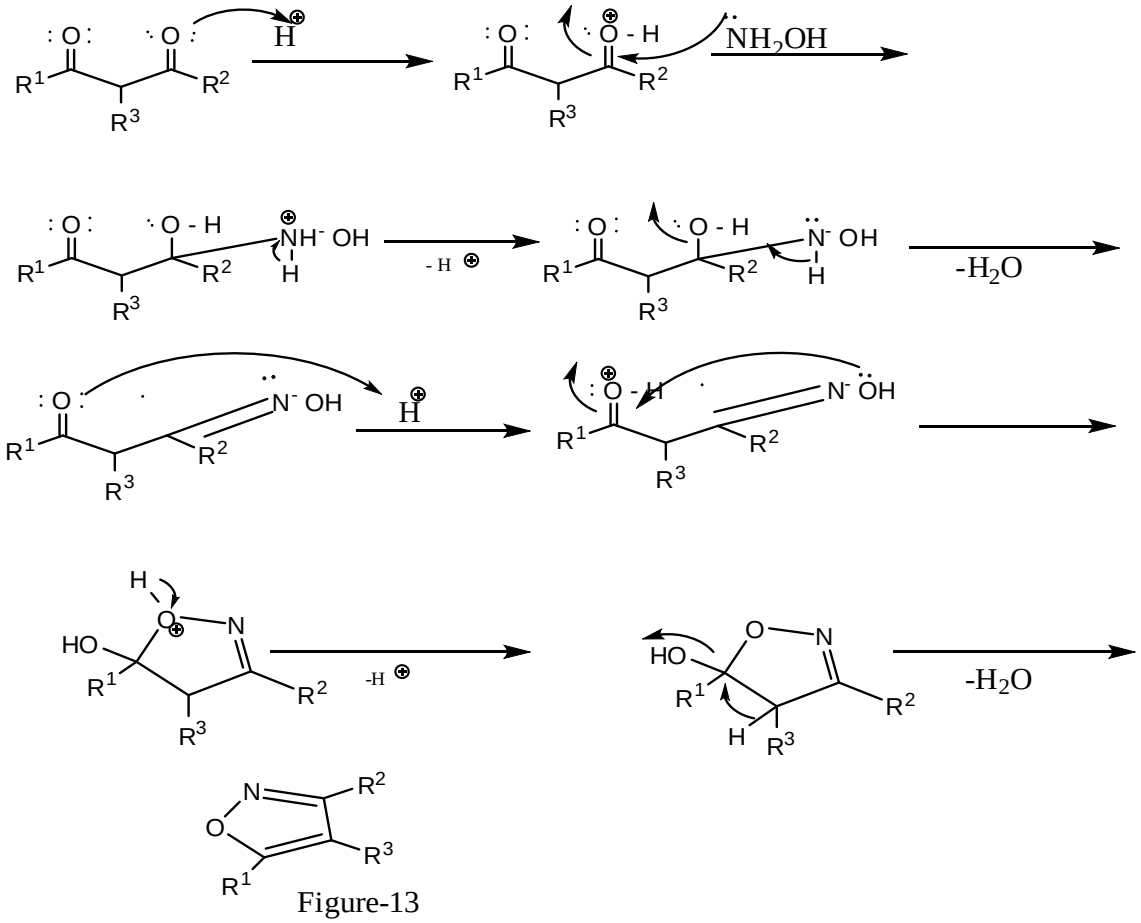


Figure 13. A one-pot green synthesis of substituted isoxazoles in an ionic liquid.



Scheme 13. Mechanism developed for one-pot green synthesis of substituted isoxazoles **13** in an ionic liquid.

2.7. Oxadiazoles

Oxadiazole nucleus is one of the most important pharmacological scaffolds. Under reaction conditions using special reagents, a general synthetic route for the synthesis of 2-alkyl/arylamino-5-alkyl/aryl-1,3,4-oxadiazoles involves the cyclization of 1-acyl-4-alkyl/aryl semicarbazides/thio semicarbazides. Synthesis of 2-amino-5-aryl-1,3,4-oxadiazoles **14** has been reported using di- (benzotriazolyl)methanimine [41] . The reaction results excellent yields with a variety of substituents like, NH_2, NO_2 or halogen in the aryl part (Scheme 14). Mechanism for the formation of **14** can be explained as (Scheme 14).

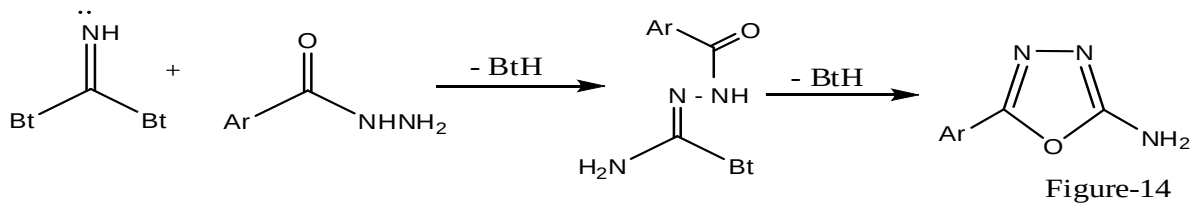
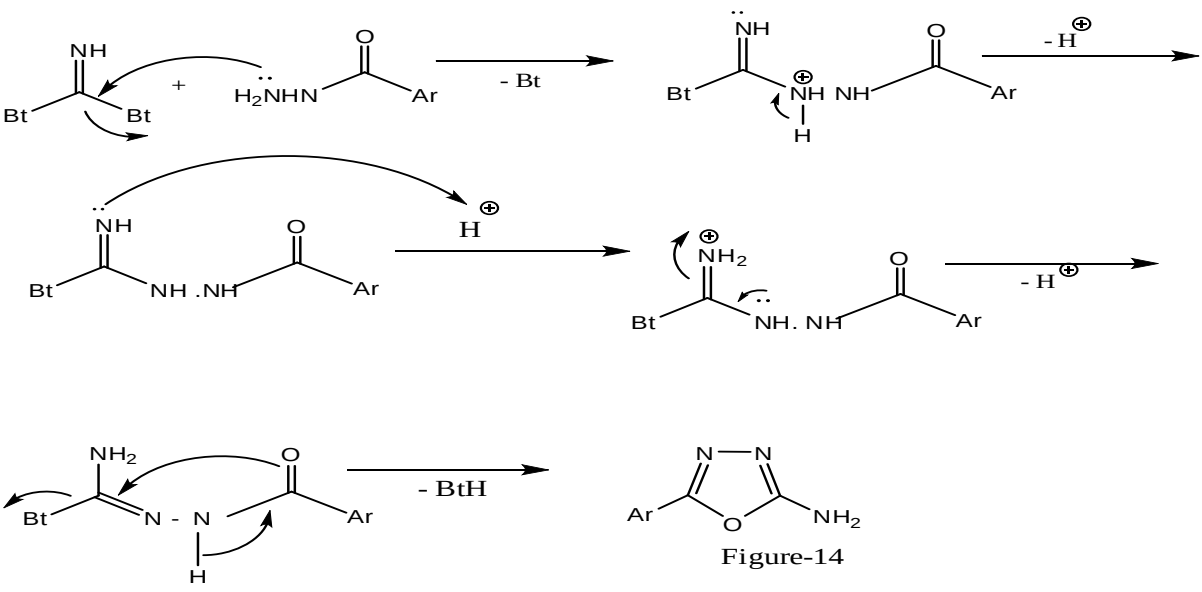


Figure 14. Synthesis of 2-amino-5-aryl-1,3,4-oxadiazoles.



Scheme 14. Mechanism developed for the synthesis of 2-amino-5-aryl-1,3,4-oxadiazoles (14).

2.8. Triazoles

Solvent free cycloaddition reaction of alkyl azides and the enol ethers has been reported to yield 1,4,5-trisubstituted 1,2,3-triazoles [42]. Regioselective synthesis of N_2-aryl triazoles **15** has recently been achieved from hydrazines and -hydroxy ketones [43] (Scheme 15).

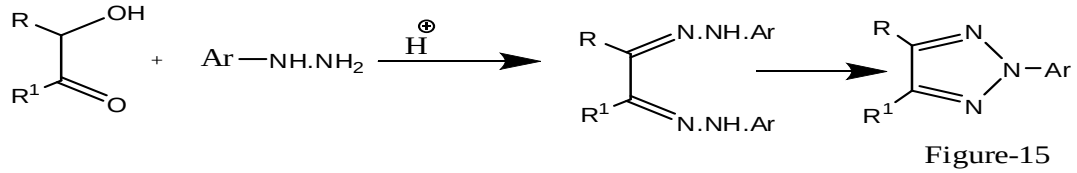


Figure 15. Regioselective synthesis of N_2-aryl triazoles.

Mechanism proposed for the formation of **15** can be rationalized as below (Scheme 15).

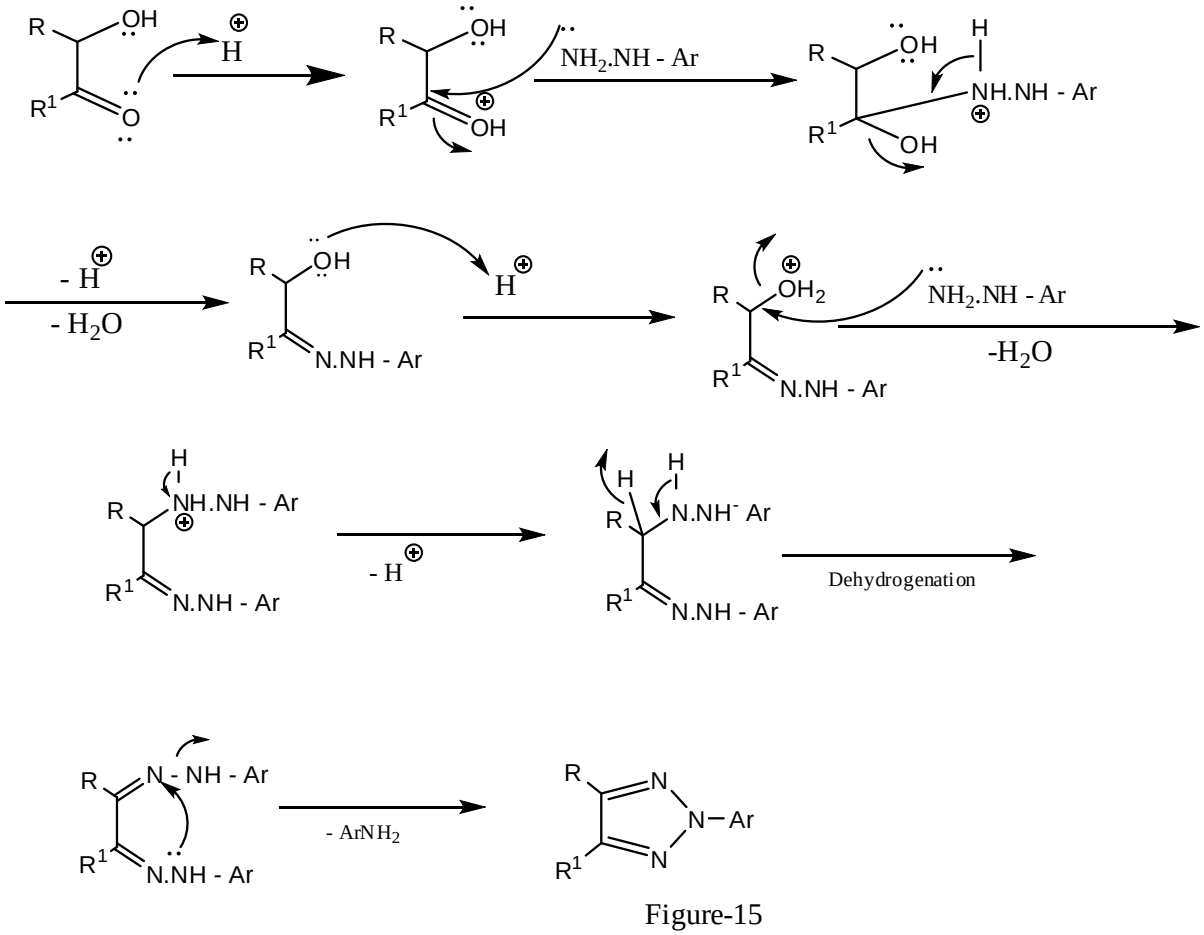


Figure 15. Proposed mechanism for regioselective synthesis of N_2-aryl triazoles (15).

3. Applications

Heterocyclic compounds display a wide range of applications in the field of chemistry and other sciences as well. They are predominantly used as pharmaceuticals, as agrochemicals and as veterinary products. They also find applications as sanitizers, developers, antioxidants, copolymers and dyestuffs. Pyrrole, an important nitrogen containing heterocycle, is found in alkaloids, haemin (colouring matter of blood), chlorophyll, bilirubin (colouring matter of bile) vitamin B_{12} etc. Furan is another member of oxygen containing five membered heterocycles.Tetrahydro furan is used as a solvent, the raw material for nylon-66, and for the production of adipic acid. Important examples of tetrahydro furan ring systems are sugars like fructose, ribose and deoxy-ribose. Thiophene and its derivatives are the sulphur containing five membered heterocyclic compounds found in petroleum and coal tar. Biotin, a B-complex vitamin, is the most important naturally occurring thiophene derivative. Anti- proliferative and antitumor activities of thiazole and oxazole have also been reported. Perhydroazoles and perhydroazines containing two and three heteroatoms are known to occupy a significant place in chemical and pharmacological research. Derivatives of pyrrolidine and imidazolidine, have been found to exhibit the antibiotic, antiviral, neurotropic, psychotropic, vasotropic, cardiotropic, anti-inflammatory and antineoplastic properties. Hydrogenated azines and azoles are known as the inhibitors of different enzymes and as plant growth regulators. Besides biological activity, perhydroazoles and perhydroazines have been found to exhibit other precious properties. Some of their substituted products are being used as electroactive, photosensitive and anticorrosive materials .These compounds are also used in the production of polymers and textiles. Heterocyclic compounds find increasing use as intermediates in organic synthesis. This is because a relatively stable ring system can be carried through a number of synthetic steps and then cleaved at the required stage in a synthesis to reveal other

functional groups. Essential diet ingredients such as thiamine, riboflavin, nicotinamide and ascorbic acid are also heterocyclic compounds.

4. Conclusions

This article summarizes the various new methods developed to synthesize a broad range of five membered heterocycle derivatives. Mechanisms for different reactions /heterocycles like Ugi reaction, Pall-Knorr synthesis, Thiazoles, Isoxazoles, Oxadiazoles or Triazoles have been developed in this article. Five membered compounds have been found extensively important for their biological activities and a variety of industrial applications. Advanced and green methods of synthesis have opened new doors for research in the field of heterocyclic chemistry.

Conflict of interest

Author declare no conflict of interest.

Data availability statement

Since it is purely a mechanism based article, so no data sharing is applicable to this manuscript.

Acknowledgements

I am grateful to Prof.K.Z.Khan for his encouragement and in-depth discussion. It was not possible to develop mechanisms for a series of unique compounds without his support. I also acknowledge my colleagues for their valuable suggestions.

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