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Synthetic Methods for the formation of Heterocyclic Compounds from Oxime Ether Derivatives

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ABSTRACT – Heterocyclic ring compounds are not only ubiquitous in prime diversity of vital natural products and synthetic pharmaceuticals and thus highly important in organic synthesis. They have an extensive range of applications. They are mainly used as veterinary products and as agrochemicals. They are also utilized as corrosion inhibitors, sanitizers, antioxidants, dye stuff and as copolymers. They are accustomed as an important source in the synthesis of bioactive organic compounds. Some natural products like antibiotics such as tetracyclines, cephalosporin, penicillin, aminoglycosides, alkaloids such as morphine, vinblastine, atropine, reserpine, tryptamine, reserpine etc. have heterocyclic constituent. Hence, synthesis of heterocyclic compounds from new procedures have been always demanding. Due to wide range of applications of heterocyclic compounds, this study is a survey of literature of last one decade, describing the methods for the heterocyclic ring formation from the oxime ether.

Keywords: *Heterocyclic compounds; Oxime ethers; Isoxazoles; Azepines; Pyrazines*

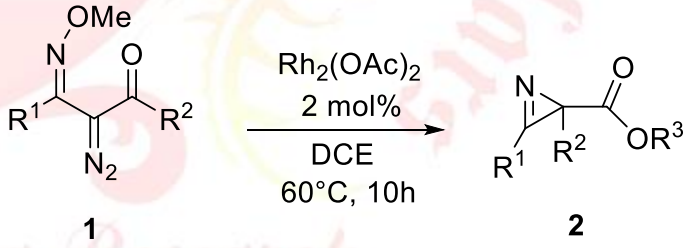
I. Introduction

Heterocyclic chemistry is an important scaffold which contributes to the medicinal, biological, pharmaceutical field including drug design, modification and expansion of biologically active compounds. These compounds have wide scope in the synthesis and process making of various types of pharmacological and biological properties. Heterocyclic rings are the major component of medicinal chemistry and mostly present in biomolecules like enzyme, vitamins, and natural products. These have shown various biological activities such as insecticidal agents,[1] anti-HIV,[2,3] anti-viral,[4-6] and anti-mycobacterial,[7-9] antifungal,[10-12] antibacterial,[13-17] antioxidant,[18-21] anticonvulsant,[22] anti-allergic,[23-24] antibiotic,[25] herbicidal activity,[26,27] anticancer activity,[28-31] and antidiabetic.[32]

Compounds having oxime ether moiety are extremely important not only for their diverse chemistry, but also for their numerous essential biological activities. It is a privilege group in chemistry due to its occurrence in a huge quantity of medicinal platforms that reveal universal range of pharmaceutical and biological activities such as antifungal,[33] antibacterial,[34] anti-viral,[35] antiprotozoan,[36] anti-inflammatory,[37] anticonvulsant,[38] anticancer,[39,40] antibiotic,[41] and many other activities.[42] Oxime ether moiety is one of the utmost versatile synthons in the field of synthetic organic chemistry.[43] Due to the wide range of applications of heterocyclic compounds formed by oxime ethers, this study presents the efficient novel methods for the formation of heterocyclic rings by utilizing oxime ethers and its derivatives.

II. Synthetic Strategies

In 2012, Jiang and his group[44] have reported a method which led to the synthesis of 2H-azirine-2-carboxylic esters **2** from rhodium catalyzed rearrangement of α-diazo-oxime ethers **1** (Scheme 1).



1 **2**

R^1 : Ar, alkyl, vinyl

R^2: alkyl, vinyl, Ar

Scheme 1: Synthesis of 2H-azirine-2-carboxylic esters

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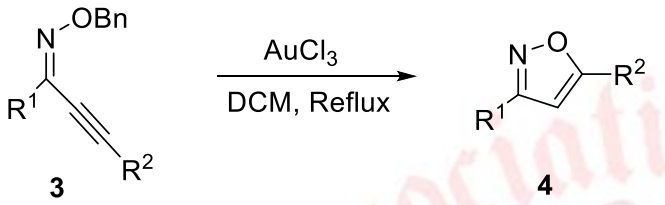
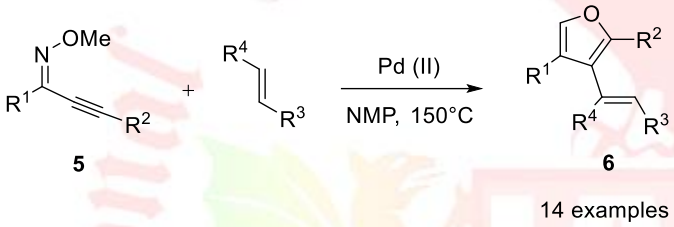
In 2011, Ueda and co-workers[45] have reported a direct and efficient method from alkynyl oxime ethers **3** for the formation of 3,5-disubstituted isoxazoles **4** *via* silver-catalysed cyclization (Scheme 2).



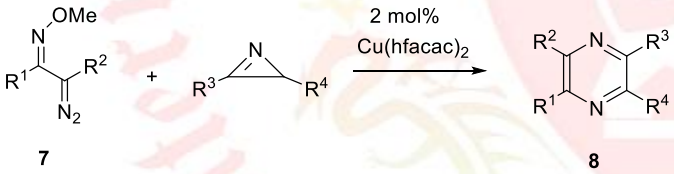
Scheme 2: Synthesis of 3, 5-disubstituted isoxazoles

She and co-worker[46] have prepared trisubstituted isoxazoles **6** from oxime ether derivative **5** by palladium catalysed cascade cyclization reaction in the presence of an olefin (Scheme 3)**.**



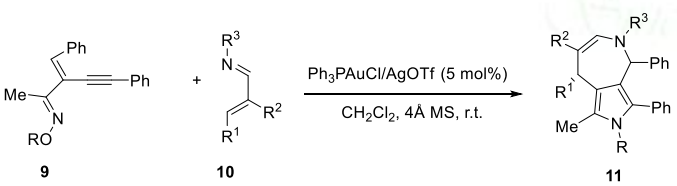
Scheme 3: Synthesis of trisubstituted isoxazoles

Loy *et al.*[47] developed an efficient synthesis of unsymmetrical pyrazines **8** from *α*-diazo oxime ether **7** (Scheme 4) *via* Cu(II) catalysed rearrangement.



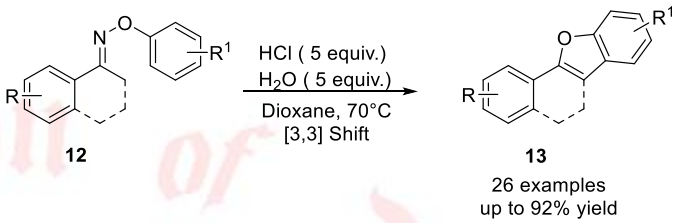
Scheme 4: Synthesis of unsymmetrical pyrazines from α-diazo oxime ether

Zhang and Zhang[48] have reported novel schematic route for formation of pyrrolo [3,4-c] azepines **11** from intermolecular diastereoselective cycloaddition of oxime **9** with α, β-unsaturated imines **10**, followed by 1,2-alkyl migration (Scheme 5) *via* gold (I) catalysis.



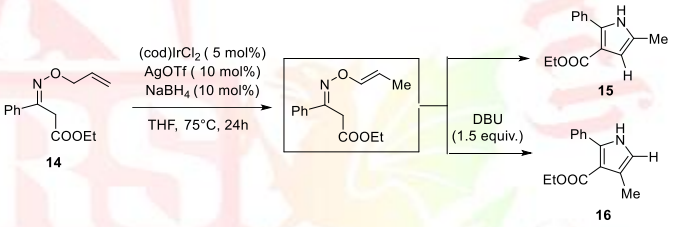
Scheme 5: Formation of pyrrolo [3,4-c] azepines

Gao and co-workers[49] reported a novel methodology for the synthesis of substituted benzo[*b*]furans **13** from *o*-aryl ketoximes **12** under acid-mediated conditions with excellent yields (Scheme 6).



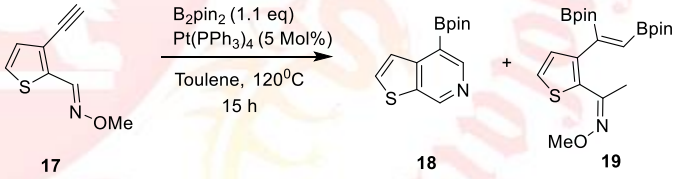
Scheme 6: Synthesis of substituted benzo[b]furans from o-aryl ketoximes

Wang *et al.*[50] has explained the formation of the 2,3,5-trisubstituted pyrroles **15, 16** from oxime ethers **14** having electron donating substituents at *α*-position *via* [3,3] and [1,3] sigmatropic rearrangements in presence of Iridium as a catalyst (Scheme 7).



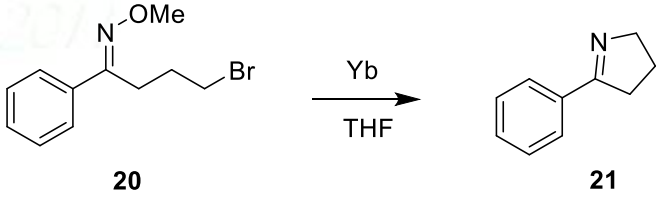
Scheme 7: Formation of the 2, 3, 5-trisubstituted pyrroles

Rado *etal.*[51] reported the synthesis of heterocyclic compounds **18, 19** by photolytically promoted *E*→*Z* isomerization and electrocyclization of *Z*-oxime **17** ethers (Scheme 8).



Scheme 8: Synthesis of heterocyclic compound 18

Wang *et al.*[52] reported the method for the formation of cyclicimines **21** by utilizing Ytterbium (0) as a mediating-metal in the intramolecular cyclization of oxime ether having bromine substituent **20 (**Scheme 9).



Scheme 9: Formation of cyclicimines from oxime ether derivative

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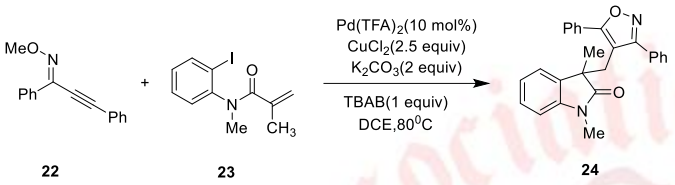
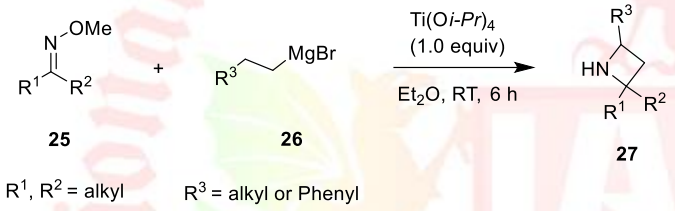
Kotipalli *et al.*[53] reported Metal-catalyzed cyclizative cross-coupling reactions by reacting alkynyl oxime ethers **22** and acrylamide **23** to form 3-((3, 5-diphenylisoxazol-4-yl) methyl)-1, 3-dimethylindolin-2-one **24** (Scheme 10).



22 **23** **24**

Scheme 10: Formation of 3-((3, 5-diphenylisoxazol-4-yl) methyl)-1, 3-dimethylindolin-2-one

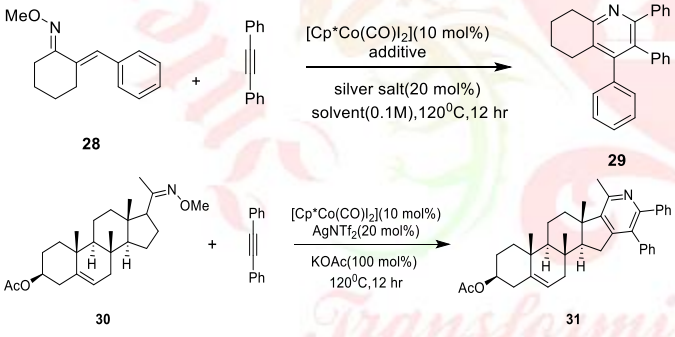
Kürti[54] and co-workers in 2019, developed a method for the synthesis of spirocyclic NH-azetidines **27** from alkyl Grignard reagents **26** and oxime ethers **25** by Ti(IV)-mediated coupling. The reaction undergoes *via* Kulinkovich-type pathway (Scheme 11).



25 **26** **27**

Scheme 11: The spirocyclic NH-azetidines formation

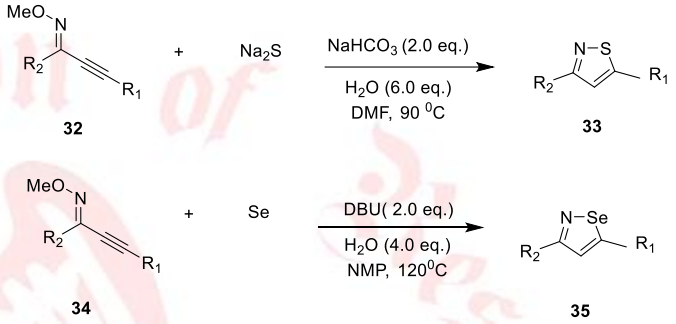
Smruti *et al.*[55] reported a redox neutral Co(III) catalyzed annulation of alkyne with α,β-unsaturated oxime ether **28** to form multisubstituted pyridines **29**. This transformation has also been applied to the modification of the dehydropregnenolone molecule **30** (Scheme 12).



28 **29** **30** **31**

Scheme 12: Synthesis of substituted pyridines

Zhang *et al.*[56] developed a new method by demethoxylative cycloaddition of alkynyl oxime ethers **32, 34** using Na_2S and Se powder, which resulted in the formation of corresponding isothiazoles **33** and isoselenazoles **35** and (Scheme 13). The reactions were carried out in presence of the base.



32 **33** **34** **35**

Scheme 13: Formation of isothiazoles and isoselenazoles

III. Conclusion

The use of oxime ethers in organic synthesis has provided efficient methods for the study of wide variety of chemical reactions, many of which are mainly the roots of synthetic organic chemistry. The methodologies discussed in this study shows that oxime ethers and its derivatives are interesting intermediates and starting materials for synthesis of bioactive heterocyclic compounds. In many cases, the use of oxime ethers by utilizing mild conditions and by opting simple procedures led to formation of heterocyclic compounds. This field of research has still further possibilities for growth and development, for extremely effective and highly versatile novel synthetic methods these compounds. We believe that this study will attract the young researchers for synthesizing novel heterocyclic compounds in the near future.

IV. Acknowledgement

The use of oxime ethers in organic synthesis has provided efficient methods for the study of wide variety of chemical reactions, many of which are mainly the roots of synthetic organic chemistry. The methodologies discussed in this study shows that oxime ethers and its derivatives are interesting intermediates and starting materials for synthesis of bioactive heterocyclic compounds. In many cases, the use of oxime ethers by utilizing mild conditions and by opting simple procedures led to formation of heterocyclic compounds. This field of research has still further possibilities for growth and development, for extremely effective and highly versatile novel synthetic methods these compounds. We believe that this study will attract the young researchers for synthesizing novel heterocyclic compounds in the near future.

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