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# Synthesis of mononuclear heterocycles via electrophilic cyclization

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| **Abstract:** | The present review covers the scientific literature of the last 15 years on electrophilic cyclization reactions which lead to the formation of a variety of mononuclear heterocyclic compounds: pyrolle, furane, pyrazole, thiazole, oxazole, isoxazole, oxaphosphole, piperidine, pyrane and oxazepane. The majority of the reviewed sources reports studies on the synthesis of five-membered heterocycles. Meanwhile the data on the obtaining of six- and more-membered moieties are lacking. We have discussed the using of different electrophilic agents, catalysts, reaction conditions and synthetic approaches, as well as the possibility of formation of saturated, partially saturated, and aromatic heterocycles. |

Reviewer #1: Please correct the typomistakes.

Dear reviwer!

Thank you for your comment. We have made all the necessary corrections.

Regards, authors

Reviewer #2:Overall recommendation - major changes, overall rating - 80. This is a valuable review that should be published after addressing the following technical issues: First, the text should be corrected by a chemist fluent in English. Alternatively, the authors should correct the following issues, provided Editor would be willing to address the remaining minor issues in the text.

1. "production" should be replaced by synthesis.
2. page 6, lines 3, 4: awkward sentence.
3. page 8, lines 8-11: fix the tenses.
4. page 15, lines 14, 15: awkward sentence.
5. page 16, lines 1-4: awkward sentence.
6. references: an awkward format with the journal abbreviations without spaces.
7. Is it required?

Dear reviwer!

Thank you for your comments. We have carefully edited our manuscript according to your notes.

Regards, authors

# Synthesis of mononuclear heterocycles via electrophilic cyclization

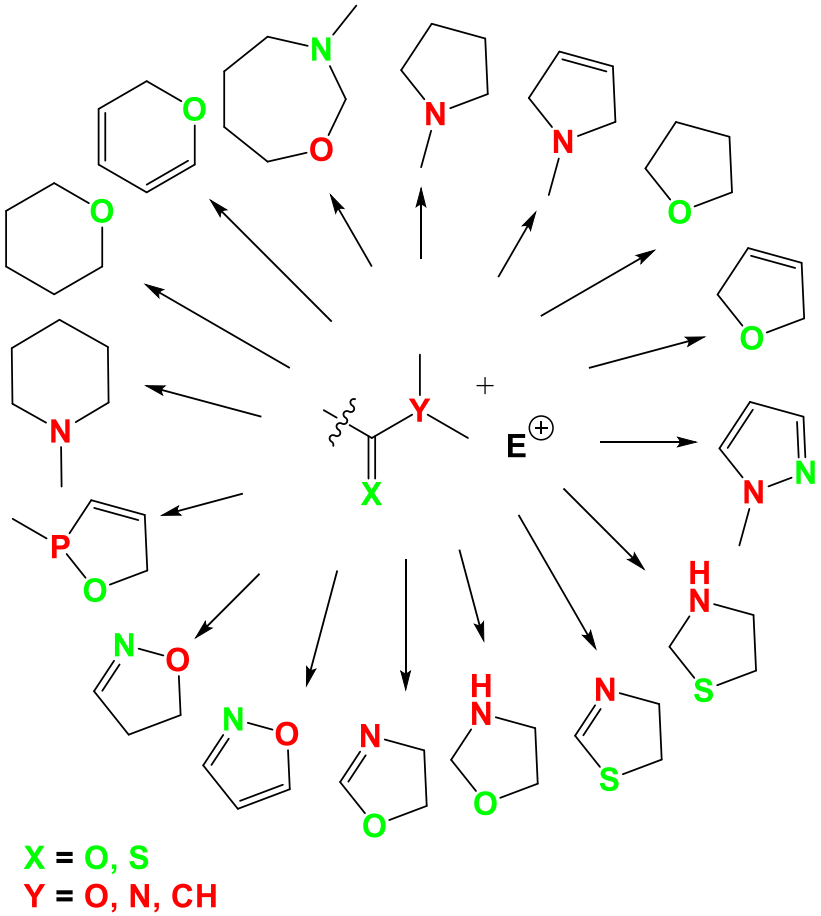
**Mikhailo Slivka[1] ● Nataliya Korol[1]**

Received: ……/Accepted …

**Abstract**

The present review covers the scientific literature of the last 15 years on electrophilic cyclization reactions which lead to the formation of a variety of mononuclear heterocyclic compounds: pyrrole, furan, pyrazole, thiazole, oxazole, isoxazole, oxaphosphole, piperidine, pyran, and oxazepane. The majority of the reviewed sources reports studies on the synthesis of five-membered heterocycles. Meanwhile the data on the obtaining of six- and more-membered moieties are lacking. We have discussed the using of different electrophilic agents, catalysts, reaction conditions, and synthetic approaches, as well as the possibility of formation of saturated, partially saturated, and aromatic heterocycles.

*Graphical abstract*




**Keywords** Heterocycles ● Electrophilic cyclizations ● Halogenation ● Reaction mechanisms ● Chemoselectivity

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# Introduction

Mono-heterocyclic compounds are known as valuable substrates which possess a variety of significant properties and they are convenient materials for further modification [1]. There are a lot of references stating the value of above heterocycles [2-14]. For example Petri and co-authors reviewed pyrrole derivatives which exhibit antitumor, antimicrobial, and antiviral activities [2-5]; anti-inflammatory and antimicrobial effects of furan natural derivatives were reported by Alizadeh and co-authors [4, 6]; Karrouchi and co-authors studied pyrazole derivatives which were considered a pharmacologically important active scaffold [2, 7], bioactive pyrazoline derivatives were reported by Nehra and co-authors [8]; antibacterial importance of thiazole and its derivatives was published by Kashyap and co-authors [3, 9]; Kakkar and Narasimhan described biological activities of oxazole derivatives [10]; the using of piperidine motif in treatment of cancer was reviewed by Goel and co-authors [11]; pharmacological interest of pyrane derivatives was reported by Asif [12]and Koop [13]; Kaur and co-authors described pharmacological and therapeutic implications of azepines [14]. There are no current sources that generalize information on the synthesis of monocyclic non-fused thiazine, thiadiazine, and oxathiazine systems, which synthesed via electrophilic heterocyclization is reported herein.

As it is known, the electrophilic intramolecular cyclization is one of the most effective and convenient synthetic technologies for the obtaining different types of heterocyclic systems. It should be noted that during the last 20 years there are only 3 sources that have systematized studies on the electrophilic cyclization. Thus Zeni and Larock [15] described data on palladium-based methodology of electrophilic cyclization of alkynes and alkenes, Godoi and co-authors [16] reported synthesis of heterocycles via electrophilic cyclization of alkynes containing heteroatom, Slivka and Onysko [17] reviewed the electrophilic cyclization method for the preparation of condensed heterocycles. The current review covers investigations on the synthetic approaches leading to the formation of mono-heterocyclic compounds via the electrophilic cyclization over the last 15 years.

## Synthesis of five-membered heterocycles with one heteroatom

### Pyrrole synthesis

Pyrrolidin-2-ones **2** were obtained from the styrylacetic acid amides **1** containing aryl or heteryl substituents in the styrene and the amide fragments [18-20]. It was established experimentally that amides **1** fully transformed into target pyrroles **2** during 1 h at heating in PPA at 105-110°C (Scheme 1).

The dominant cyclization route is the attack of $C^+$-electrophile (formed after the protonation of the multiple bond) on the amide nitrogen atom.

< Scheme 1 >

It has been determined that anilides **1** react with sulfenyl chlorides **3** in nitromethane or acetic acid in the presenceof an equimolar amount of lithium perchlorate as a “doping additive” to form pyrrolidin-2-ones **4** in a good yield [21, 22] (Scheme 2). The process is implemented via the scheme, which contains the pre-dominant formation of the episulfonium intermediate stabilized by the perchlorate-anion followed by *5-endo*-cyclization onto the nitrogen atom of the amide group.

< Scheme 2 >

A tandem sequence of 5-*endo* halolactamization and direct C-H oxidative functionalization of amides of substituted allylacetic acid **5** with the using of halogens as electrophiles lead to the synthesis of *β*-halopyrrolidinones **7** with satisfactory to excellent yields (Scheme 3) [23]. The reactions of 4-mono- or 4-unsubstituted 2,3-alkadienamides **6** with $CuX_2$ also afforded 5-hydroxypyrrol-2(5*H*)-ones **7** via the sequential

lactamization and γ-hydroxylation process in aqueous THF [24] (Scheme 3). Authors [23] proposed the mechanism for the formation of 7 (Scheme 3). Firstly, the electrophilic attack on the olefin gives intermediates that through the amide nitrogen give the corresponding lactam. Elimination of hydrogen halide generates enamide, which undergoes allylic oxidative functionalization to yield a heterocyclic ammonia cation, further treatment with water affords pyrrolidinone **7**. Initially, an electrophilic attack on the olefin gives an intermediate product, which through the amide nitrogen gives the corresponding lactam. Furthermore the elimination of hydrogen halide generates an enamide, which is subjected to allylic oxidative functionalization to yield a heterocyclic ammonia cation, the subsequent treatment of which with water affords pyrrolidinone **7**.

< Scheme 3 >

A selenium-promoted electrophilic cyclization of *N*-aryl(alkyl) amides **8**, allowing the synthesis of 3-organoselenyl spiro[4,5]trienones **9** via a 5-*endo*-dig *ipso*-mode, was investigated with the use of diaryldiselenides as the selenium precursors and inexpensive $K_2S_2O_8$ as the oxidant [25] or phenyl(butyl)selenyl bromides as the electrophilic source [26] (Scheme 4).

< Scheme 4 >

**Furan synthesis**

Anilides of styrylacetic acids **1** were converted to furanone **10** with considerable yields (Scheme 5) [18]. The attack on the amide oxygen atom was activated by the presence of fluoroaryl substituents of compounds **1**.

< Scheme 5 >

When the styrylacetamides **1** or allylacetamides **13** reacted with arylsulfenyl chlorides **3** in acetic acid in the presence of $LiClO_4$ as a "doping" agent, a regio- and stereoselective intramolecular cyclization have occurred at the oxygen atom of the amide group. As a result tetrahydrofuran-2-iminium perchlorates **11** [27] or *N*-alkyl(aryl)-*N*-[5-[(arylsulfanyl)methyl]dihydrofuran-2(3*H*)-ylidene]aminium perchlorates **14** [28] formed (Scheme 6). 5-Aryl-4-(arylthio)tetrahydrofuran-2-ones **12** may be obtained after chromatographic purification the reaction mixture on silica gel [20, 22] (Scheme 6). The episulfonium ion attacks the carbonyl oxygen atom, and this pathway involves intermediate formation of the corresponding iminium salt, which further undergoes hydrolysis to lactones **12** (Scheme 6).

< Scheme 6 >

The interactionbetween 4,4-disubstituted 2,3-alkadienamides **15** and copper(II) halides leads to formation of 2,5-dihydrofuranes **16** in high yields (Scheme 7) [24]. The similar synthesis of substituted 2,5-dihydrofuranes **18** was provided via the reaction of 4-phosphorylated 5-hydroxypenta-2,3-dienoates **17** with electrophiles involving 5-*endo*-*trig* cyclization (Scheme 7) [29].

< Scheme 7 >

# Synthesis of five-membered heterocycles with two heteroatoms

## Pyrazole synthesis

A simple and efficient method for the synthesis of 4-chalcogenyl pyrazoles **20** has been developed. According to the study [30], the selenium electrophiles were generated in situ by the reaction of diorganyldiselenides with oxone in ethanol and were employed in the selenylation/cyclization of alkynylhydrazones **19**, giving the compounds **20** in moderate to excellent yields (Scheme **8**). The second approach [31] also includes in situ generation of S(Se)-electrophiles from the readily available NCS(Se) and arythiols with

further cyclization of *α*,*β*-alkynichydrazones **19** which results in synthesis of 4-chalcogenyl pyrazoles **20** (Scheme 8).

< Scheme 8 >

**Thiazole synthesis**

Compounds **21** undergo cyclization with the formation of 2-ylidene-substituted 5-halogenomethylthiazolidine hydrohalides **22** [32, 33] or 5-halogenomethyldihydrothiazole hydrohalides **23** [34, 35] under the action of halogens, thionyl chloride, or concentrated hydrochloric acid (Scheme 9).

< Scheme 9 >

**Oxazole synthesis**

Carboxamides **24** react with polyphosphoric acid [36] to afford the dihydrooxazole ring containing a methyl group in the 5-position of target oxazolines **25** (Scheme 10). The electrophilic cyclization of carboxamides **24** to the oxazolines **26** is also possible via the action of *N*-halosuccinimides [36], or via arylsulfenylation [37], or selenide-catalyzed trifluoromethylthiolation [38] (Scheme 10).

< Scheme 10 >

A Lewis acid catalyzed synthesis of oxazoles **29** was reported from readily accessible alkynols **27** and N,O-aminols **28** [39] (Scheme 11). This method operates by an electrophilic carbofunctionalization pathway under mild conditions.

< Scheme 11 >

**Isoxazole synthesis**

An efficient method for the synthesis of 4-sulfenyl isoxazoles **31** has been developed via $AlCl_3$-mediated electrophilic cyclization/sulfenylation of 2-alkyn-1-one *O*-methyloximes **30** (Scheme 12). Remarkably, *N*-arylsulfanylsuccinimides are employed as electrophiles for the construction of 4-arylsulfanyl isoxazoles; 4-alkylsulfanyl isoxazoles are accessed with employing dialkyl disulfides as electrophiles [40]. The activation of *N*-arylsulfanylsuccinimides or disulfides with $AlCl_3$ would give the sulfenium cation, which could react with C-C triple bond to form an intermediate. Subsequently, intramolecular cyclization via nucleophilic attack of oxygen to the activated $C_{sp}$ results in the formation of the corresponding

intermediate, which undergoes demethylation to afford the desired 4-isoxazolyl sulfides **31** (Scheme 12).

< Scheme 12 >

Chalcogen-functionalized isoxazolines **33** and **34** were prepared by the reaction of *β,γ*-unsaturated oximes **32** with selenium and tellurium electrophiles in good yields after 1 hour at room temperature (Scheme 13). Selenium- and tellurium-containing isoxazolines **33** were obtained under the action of corresponding arylchalcogen halides, while the (bis)isoxazoline ditellurides **34** were synthesized by using the tellurium tetrachloride [38].

< Scheme 13 >

**Oxaphosphole synthesis**

The competitive electrophilic cyclization of phosphorylated dienoates **17** involving 5-*endo*-*trig*-cyclization was reported [29, 42]. The reaction produces oxaphospholes **35** in moderate yields (Scheme 14). It was noted, that the reaction stops in the stage of formation of the cyclic phosphonium salts **36** if Y=Ph [29].

< Scheme 14 >

## Synthesis of six-membered heterocycles with one heteroatom

### Piperidine synthesis

*N*-Alkyl(aryl)amides of cinnamylacetic acid **37** with arylsulfenyl chlorides **3** are subjected to selective cyclization into 5-arylsulfanyl-6-phenylpiperidin-2-ones **38** (Scheme 15) [43, 44]. The reaction can be carried out in acetic acid mediumin the presence of lithium perchlorate [43] or in chloroform in the absence of lithium perchlorate [44]. In the course of the intramolecular electrophilic cyclization the episulfonium ring of the intermediate is attacked by the nitrogen atom to the formation of compounds **38**.

< Scheme 15 >

### Pyrane synthesis

The reaction between arylsulfenyl chlorides **3** and amides **37** at the nitrogen atom selectively resulted in 5-arylsulfanyl-6-phenyltetrahydropyran-2-iminium perchlorates **39** in good yields (Scheme 16) [43]. Reaction mechanism is characterized by the nucleophilic attack of the oxygen atom of the initial amides.

< Scheme 16 >

Sonogashira coupling reaction with N-substituted 3-iodovinylic ester **40** leads to the formation of corresponding intermediate that undergoes intramolecular iodocyclization (Scheme 17) resulted in substituted amino-containing 2*H*-pyran-2-ones **41** in good yields [45].

< Scheme 17 >

## Synthesis of seven-membered heterocycles with two heteroatoms

### Oxazepane synthesis

Substituted 1,3-oxazepane **43** was obtained in excellent yield via Lewis-catalyzed electrophilic carbofunctionalization pathway under mild conditions (Scheme 18) [39].

< Scheme 18 >

This protocol has been already mentioned for the synthesis of oxazoles (Scheme 11).

## Conclusion

The present review summarizes the literature data for the last 15 years on electrophilic cyclization reactions leading to the formation of mono-heterocyclic systems. The reaction mechanism and chemoselectivity are discussed. The variety of starting materials for further cyclization and the diversity of used electrophilic agents were also highlighted. Thus, substituted unsaturated acid amides, acid esters, hydrazones, isothiocyanates, and oximes were found among the classes of compounds that underwent the cyclization process. Polyphosphoric acid, thionyl chloride, halogens, alkyl(aryl)chalcogen halides, chalcogen tetrahalides, copper(II) halides, N-substituted succinimides, or N,O-aminoles can be chosen as electrophilic reagents. All obtained heterocycles are attractive to further investigation with special attention to their possible application.

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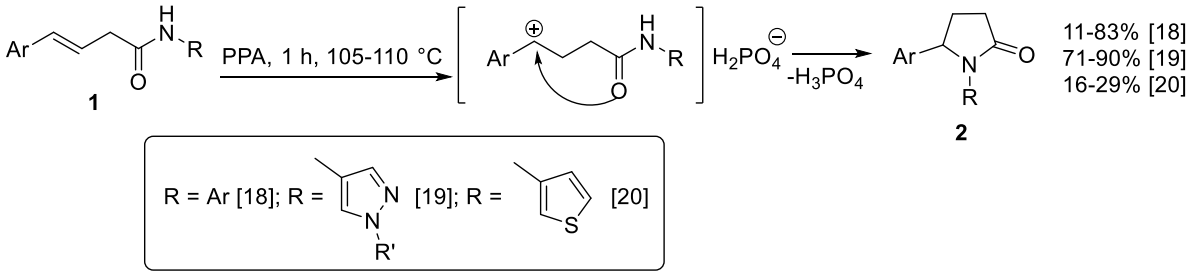
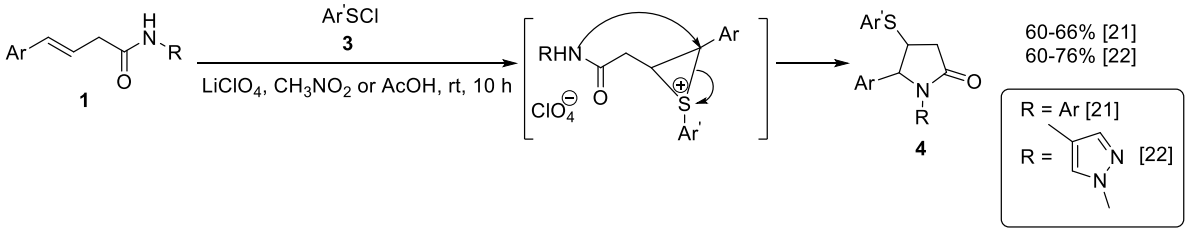
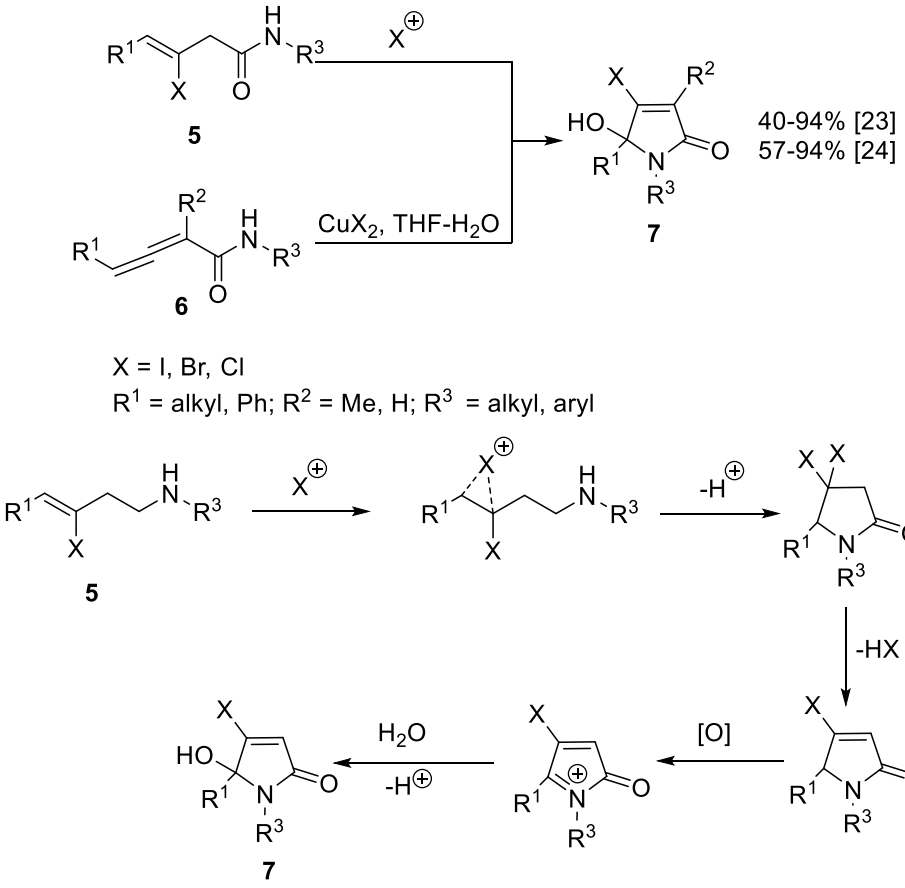
*Scheme 1*



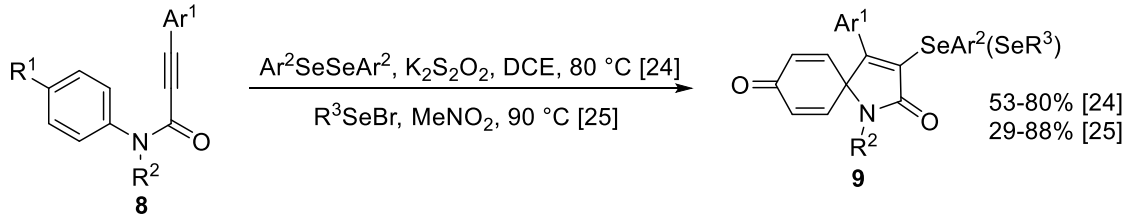

*Scheme 2*



*Scheme 3*

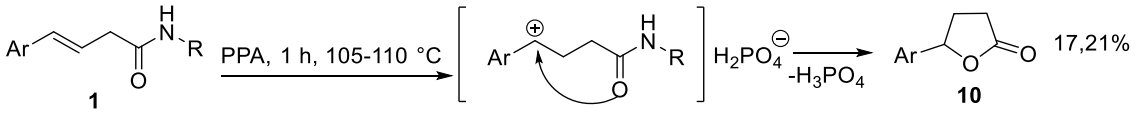



*Scheme 4*

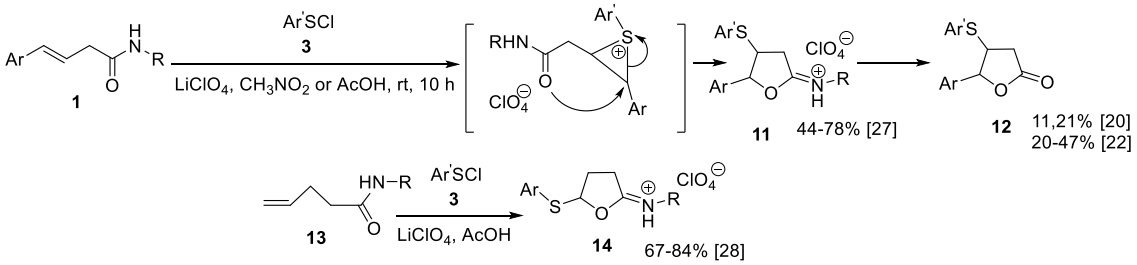



$R^1$ = OMe, F; $R^2$ = Me, Bu; $R^3$ = aryl, Bu

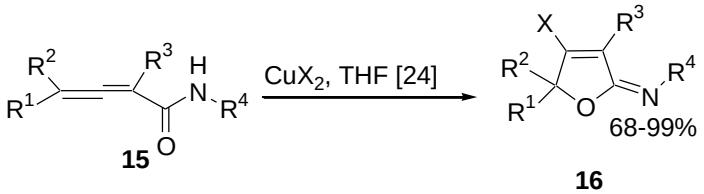
*Scheme 5*




*Scheme 6*

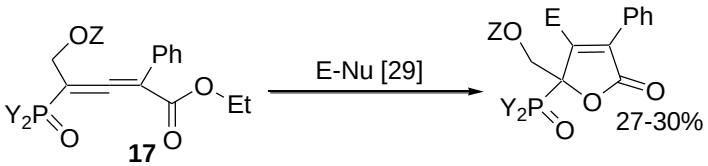



*Scheme 7*




X = Br, Cl

$R^1$ = Me, Ph; $R^2$ = Me, H ; $R^3$ = H, Bn, Me; $R^4$ = Bn, *n*-Bu



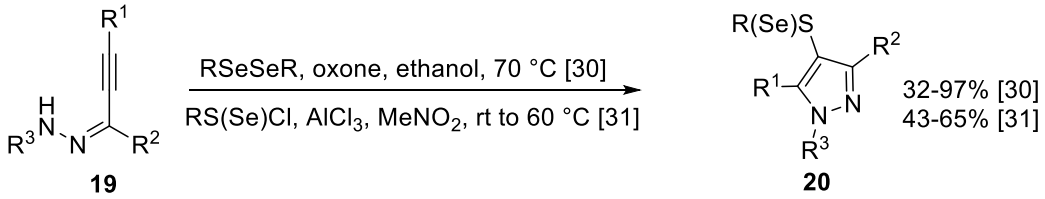

E = Cl, Br, PhS, PhSe

Nu = Cl, Br

Y = MeO, Ph

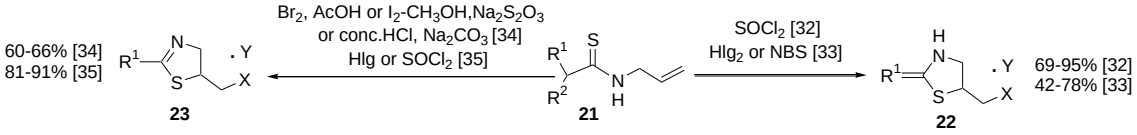
Z = H, THP

*Scheme 8*




$R^1$ = alkyl, aryl; $R^2$ = H, alkyl, aryl; $R^3$ = aryl; R = alkyl, aryl

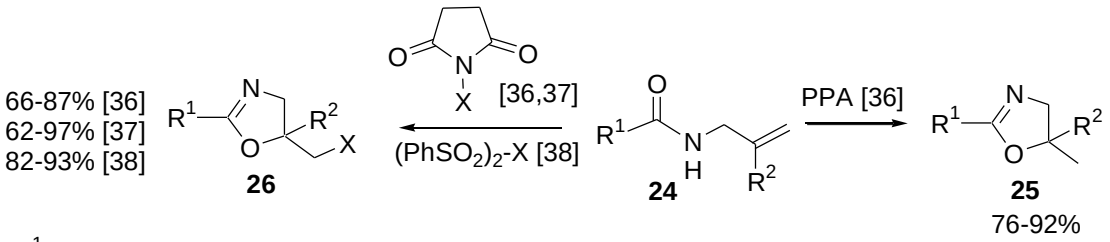
*Scheme 9*




$R^1$ = NH-Het, Het, H, C(O)OEt, Ac, CN
$R^2$ = C(O)OEt, Ac, CN
X = Cl, I, Br
Y = HCl, $HBr_3$, $HI_3$

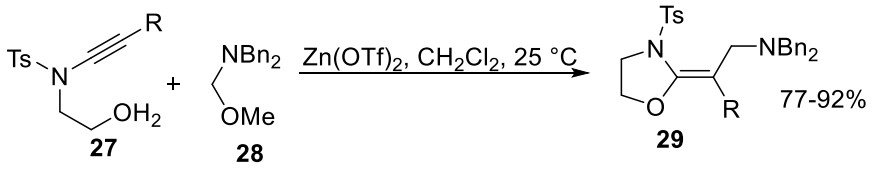
$R^1$ = Het-N=

*Scheme 10*



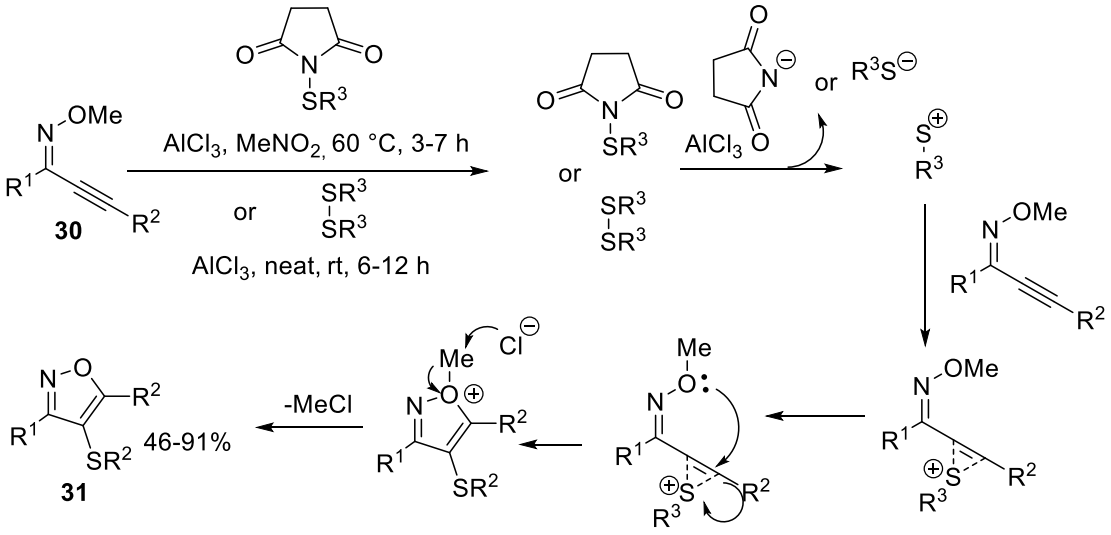

$R^1$ = Het, Ar
$R^2$ = H, Ar
X = I, Br, SPh, $SCF_3$

*Scheme 11*



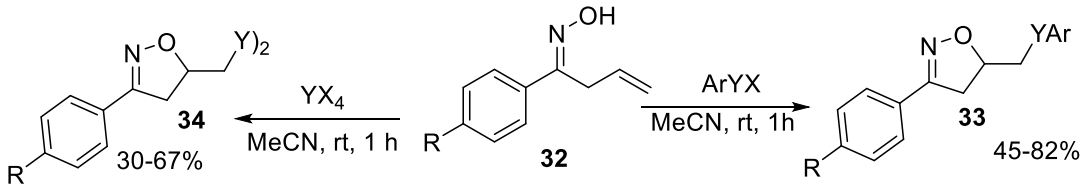

R = alkyl, aryl

*Scheme 12*



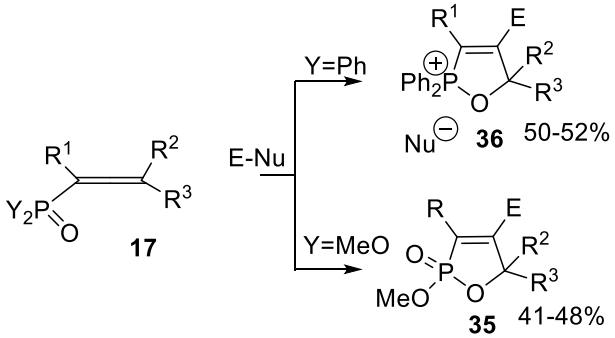

$R^1$ = alkyl, aryl; $R^2$ = alkyl, aryl, Het; $R^3$ = aryl, Et, Me

*Scheme 13*



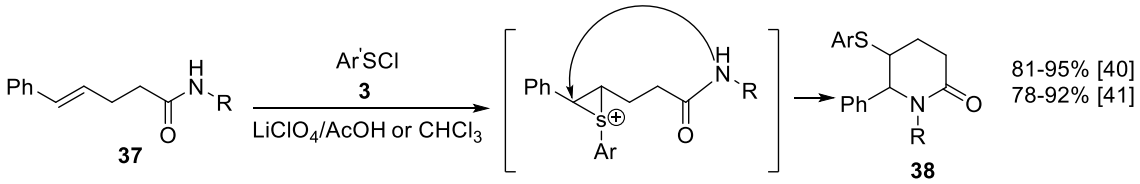

R = H, Br, Cl, F, Me, MeO
Y = Se, Te
X = Cl, I

*Scheme 14*

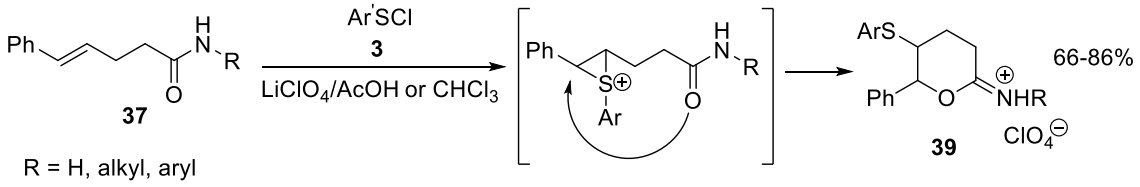



E = Cl, Br, MeS, PhS, PhSe
Nu = Cl, Br
Y = MeO, Ph
Z = H, THP
$R^1$ = $CH_2OZ$, H, Pr, Bu, Ph
$R^2$ = Me, Ph
$R^3$ = C(O)OEt, $C(Me)_2CO_2Me$, $CH(Et)_2CO_2Et$

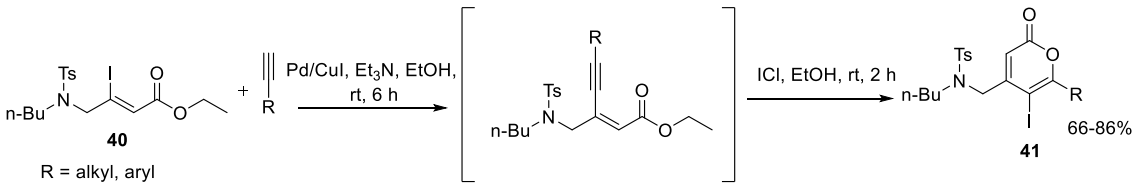
*Scheme 15*




*Scheme 16*




*Scheme 17*



*Scheme 18*