Review

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A fascinating decade for the synthesis of 1,2-azoles

Abstract: 1,2-Azoles comprising pyrazoles, isoxazoles, and isothiazoles have occupied a distinctive position in the design and synthesis of novel biologically active compounds that exert remarkable pharmaceutical activities as medicines and agrochemicals. As a consequence, there has been an increasing interest among synthetic organic/medicinal chemists in the development of methodologies for the rapid access to these heterocycles. In this review, we have summarized the most significant advances in the construction of functionalized pyrazoles, isoxazoles, and isothiazoles reported in the literature up to 2012.

Keywords: 1,2-azoles; isothiazoles; isoxazoles; pyrazoles; synthesis.

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Introduction

Heterocycles are of immense importance in the design and discovery of new compounds for pharmaceutical applications. Among them, functionalized pyrazoles, isoxazoles, and isothiazoles are present in a myriad of medicinally important natural and synthetic compounds that have a broad and interesting range of biological activities including antibacterial [1], antiviral [2], antitumor [3], antidiabetic [4], anticancer [5], anti-inflammatory [6], antipyretic [7], and HIV-1 protease inhibitory activity [8]. Some representative molecules of this structural motif are shown in Figures 1 and 2. Therefore, synthetic methodologies allowing the rapid access to these heterocycles are highly desirable in organic synthesis and chemical biology/medicinal chemistry. Some review articles have been published on pyrazole chemistry in earlier literature [9, 10]; however, to the best of our knowledge there is no recent literature comprising all three 1,2-azoles, that is, pyrazoles, isoxazoles, and isothiazoles. This review is intended to provide updated information regarding the available methodologies (focusing on the period 2002–2012) in the synthesis of functionalized pyrazoles, isoxazoles, and isothiazoles.

1*H*-Pyrazoles

A simple methodology for the one-pot synthesis of 1,3,5-trisubstituted pyrazoles was reported by Armstrong et al. [11] in 2005. The protocol involves the electrophilic amination of primary amines with *N*-Boc-oxaziridine under metal-free conditions that affords synthetically versatile, mono-Boc-protected hydrazines. Condensation of the hydrazines with symmetrical 1,3-diketons affords the 1,3,5-trisubstitutes pyrazoles (Scheme 1).

In 2006, Boruah and coworkers [12] reported on a novel one-pot method for pyrazoles by the reaction of β-formyl enamides **4** with hydroxylamine hydrochloride catalyzed by potassium dihydrogenphosphate in acid medium. The reactions of a broad range of β-formyl enamides such as steroidal, alicyclic, aliphatic, and aromatic β-formyl enamides give rise to the corresponding pyrazoles in high yields (Scheme 2).

Silver(I)-catalyzed regioselective synthesis of 1,3- and 1,5-substituted pyrazoles was reported by the Chung group in 2008 [13]. Under mild reaction conditions, intramolecular cyclization of propargyl *N*-sulfonylhydrazones **8** in the presence of 5 mol% AgSbF$_6$ as catalyst in dry dichloromethane affords 1,3,5-substituted pyrazoles **9** at room temperature. The process involves an intermolecular migration of the sulfonyl group through the formation of a tosyl anion and an electron-deficient pyrazolyl iminium cation as anion pair. *N*-Monosubstituted pyrazoles ($R^1 = R^2 = H$) are obtained in high yield from a variety of aryl, alkenyl, and styryl hydrazones. The introduction of a methyl group at the propargylic position in the styryl hydrazine **8** slightly decreases the yield of the reaction. Moreover, 1,3,5-substituted pyrazoles **9** are obtained in
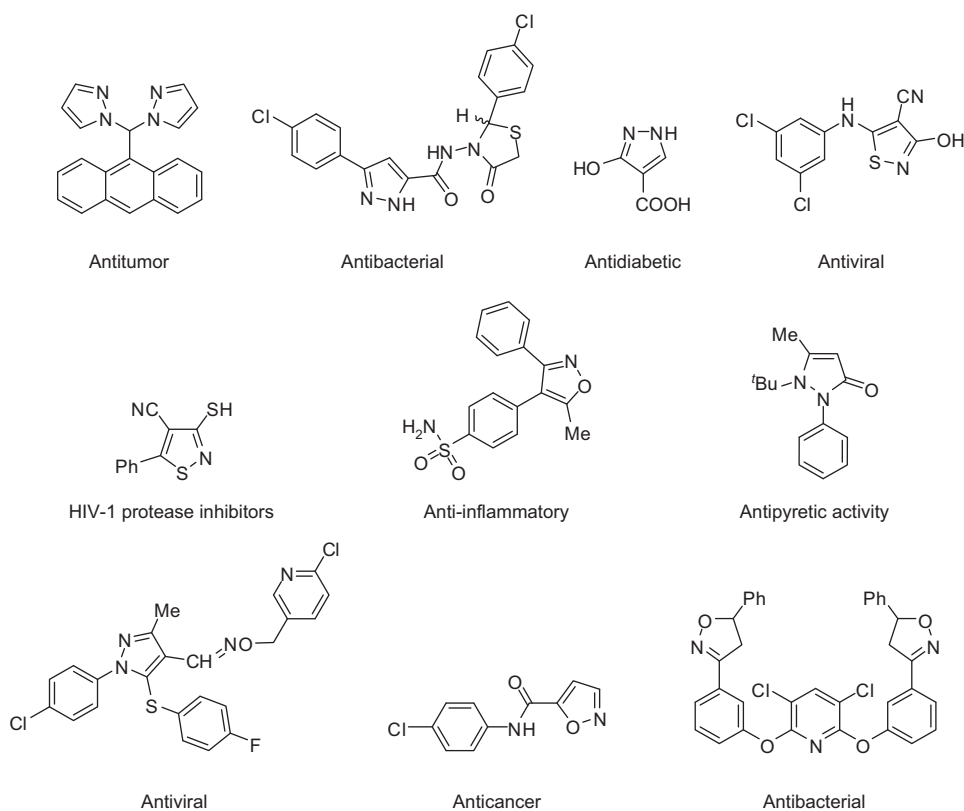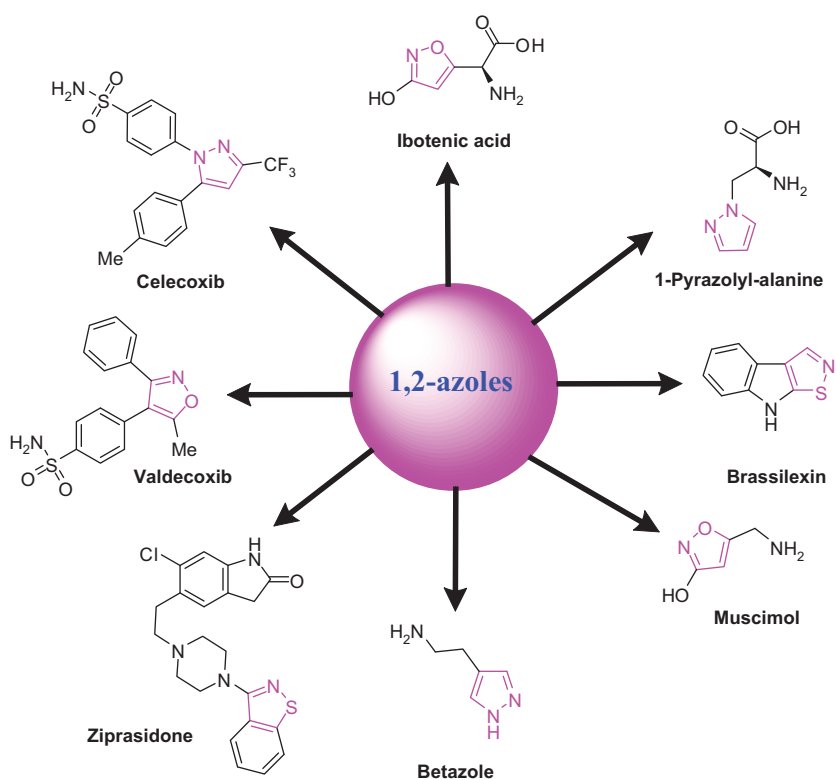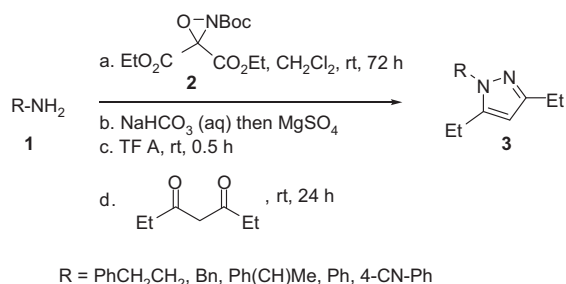
Figure 1 Biologically important 1,2-azoles.

Figure 2 1,2-Azoles in natural products and pharmaceutical drugs.

Scheme 1

R = PhCH$_2$CH$_2$, Bn, Ph(CH)Me, Ph, 4-CN-Ph

Scheme 3

R^1 = H, Me   R^2 = H, Me, Ph   R^3 = Ph, styryl, alkyl

acceptable yield starting from 4-methoxystyryl hydrazone (Scheme 3).

An efficient, rapid, and general one-pot synthetic protocol of 3,5-, 1,3,5-, 3,4,5-, and fused ring-substituted pyrazoles **13** was reported by Heller and Natarajan in 2006 (Scheme 4) [14], starting from enolizable ketones **10**, acid chlorides **11**, and hydrazines. In the methodology, the 1,3-diketones (not isolated) so produced are converted *in situ* into pyrazoles by treatment with the appropriate hydrazines. A wide range of functional groups such as nitriles, alkyl halides, and electrophiles with enolizable moieties are tolerated in the reaction. The reaction between cyclic saturated ketones and acid chlorides affords fused pyrazoles in good yields. Moreover, both benzyl *p*-chlorophenyl ketone and *n*-butyl *p*-chlorophenyl ketone are coupled with *p*-methoxybenzoic acid chloride to give the corresponding 1,3-diketones, which are then condensed with hydrazine to afford the corresponding 3,4,5-substituted pyrazole derivatives.

Subsequently, Jiang et al. [15] reported on an efficient and general one-pot procedure for the synthesis
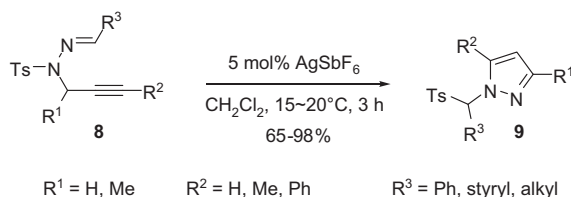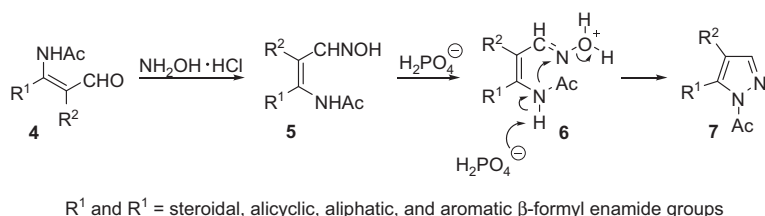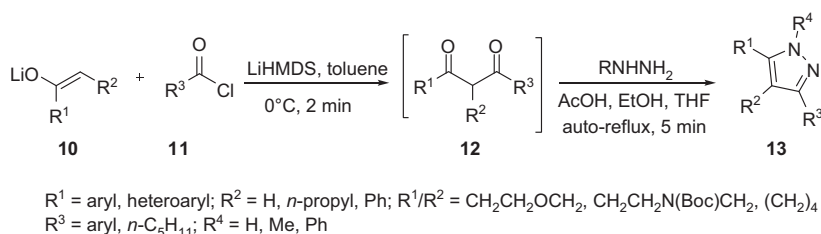
of pyrazoles from acid chlorides, terminal alkynes, and hydrazines. Acid chlorides **14** undergo coupling with terminal alkynes **15** to give α,β-unsaturated ynones which, *in situ*, are converted into pyrazoles by the cycloaddition of hydrazines catalyzed by Pd(PPh$_3$)$_2$Cl$_2$/CuI. 3,5-Diaryl-1*H*-pyrazoles **16** are obtained in moderate to good yields from aryl chlorides and aryl terminal alkynes. However, the use of aliphatic alkyne, 1-octyne, leads to its corresponding pyrazole derivative in low yield (Scheme 5).

Fully substituted pyrazoles have received a great deal of attention as they exhibit useful pharmacological and agrochemical properties. In 2011, Wang et al. reported on a methodology in which tetrasubstituted pyrazole **19** has been obtained from 2-azidoacrylate **17** and hydrazine **18** via [3 + 2] cycloaddition reaction in the presence of triethylamine in moderate to good yields with high regioselectivity (Scheme 6) [16].
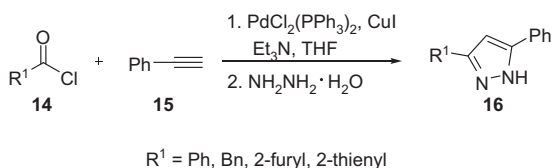
Soon after, Zora and coworkers [17] reported on the synthesis of highly substituted 4-iodopyrazole derivatives by electrophilic cyclization of acetylenic aldehydes and ketones through the intermediary of hydrazones in the presence of molecular iodine. The mechanism proposed by the authors involves an electrophilic addition of I$^+$ to
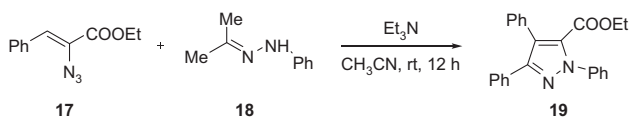
R^1 and R^1 = steroidal, alicyclic, aliphatic, and aromatic β-formyl enamide groups

Scheme 2

R^1 = aryl, heteroaryl; R^2 = H, *n*-propyl, Ph; R^1/R^2 = CH$_2$CH$_2$OCH$_2$, CH$_2$CH$_2$N(Boc)CH$_2$, (CH$_2$)$_4$
R^3 = aryl, *n*-C$_5$H$_{11}$; R^4 = H, Me, Ph

Scheme 4

Scheme 5

R^1 = Ph, Bn, 2-furyl, 2-thienyl

Scheme 6

Scheme 8

R^1 = Ph, 3-pyridyl, 2-furyl
R^2 = H, Me; R^3 = H, Me

Scheme 9

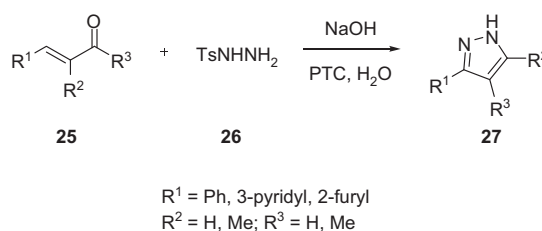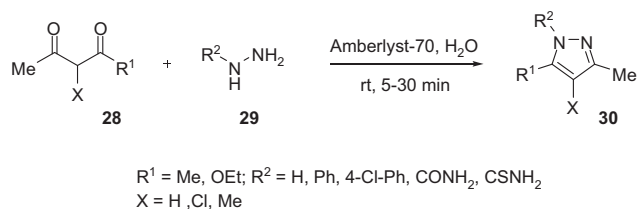R^1 = Me, OEt; R^2 = H, Ph, 4-Cl-Ph, CONH$_2$, CSNH$_2$
X = H ,Cl, Me

the alkyne, leading to an iodonium ion that undergoes an electrophilic cyclization via nucleophilic attack of the secondary nitrogen atom to furnish protonated pyrazole **23**. Finally, deprotonation with base affords 4-iodopyrazole derivative **24** (Scheme 7).

In recent years, interest in greener technologies has favored the development of using alternative reaction media that circumvent the problems associated with many of the traditional volatile organic solvents. Adopting this eco-friendly technology, Yu and coworkers in 2011 [18] developed a protocol for the synthesis of highly functionalized pyrazole **27**. Thus, condensation of α,β-unsaturated carbonyl compound **25** with tosyl hydrazide **26** in water affords trisubstituted pyrazole **27** in high yield (Scheme 8).

Another strategy based on an environmentally benign, eco-friendly approach for the synthesis of pyrazoles has been developed by Chandak et al. [19]. The method involves the condensation of hydrazine/hydrazide **29** with 1,3-diketone **28** using Amberlyst-70 as a recyclable catalyst which proceeds efficiently at room temperature in aqueous medium without the use of any organic solvent affording substituted pyrazole **30** (Scheme 9).

Very recently, Dissanayake and Odom [20] reported on an efficient three-component, one-pot reaction for the preparation of substituted pyrazoles. The strategy involves a simple titanium complex-catalyzed three-component coupling of alkynes **32**, isonitriles **33**, and monosubstituted hydrazines **31** to provide substituted pyrazoles **34** in a single step. This is the first reported protocol where transition metal efficiently catalyzes the coupling to produce a single regioisomer in high yield (Scheme 10).
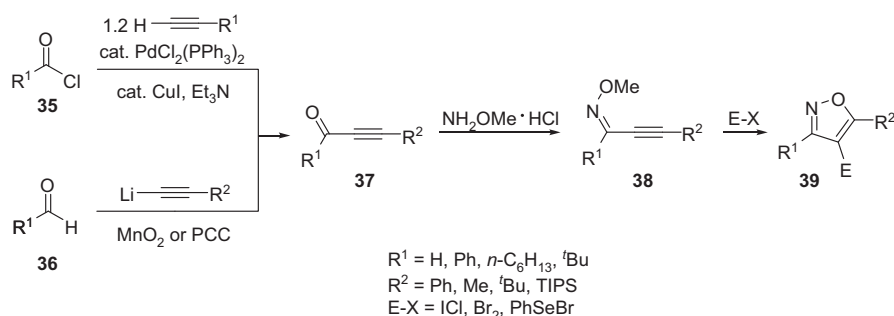
R = CH$_2$SiHMe$_3$, (CH$_2$)$_3$OTBS
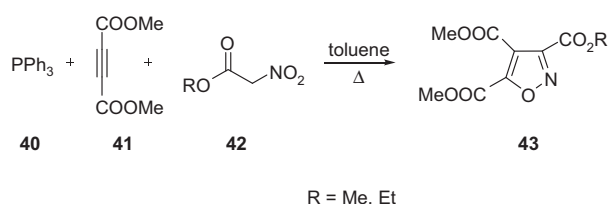pypyr = 2-(2′-pyridyl)-3,5-dimethylpyrrole
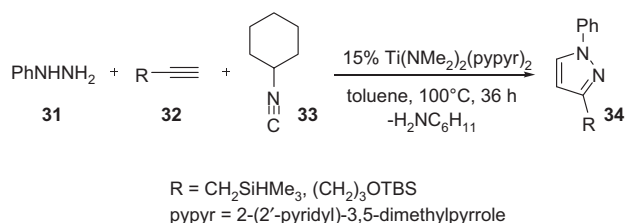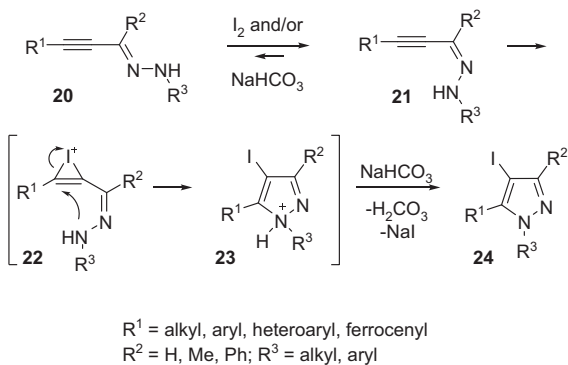
Scheme 10

Isoxazoles

The electrophilic cyclization of functionally substituted alkynes has attracted much attention due to its wide utility in the preparation of a range of useful, functionally substituted heterocycles. In 2005, Waldo and Larock [21] reported on an efficient protocol in which the reaction of 2-alkyn-1-one O-methyl oximes **38** with ICl, I$_2$, Br$_2$, or PhSeBr affords 3,5-disubstituted 4-halo(seleno)isoxazoles **39** in good to excellent yields under mild reaction conditions (Scheme 11).

R^1 = alkyl, aryl, heteroaryl, ferrocenyl
R^2 = H, Me, Ph; R^3 = alkyl, aryl

Scheme 7

Scheme 11

R = Me, Et

Scheme 12

Currently, one-pot reactions are gaining prominence due to their environmental advantages and cost effectiveness. In 2006, Yavari and Moradi [22] reported on a one-pot strategy for the synthesis of isoxazoles **43** from dialkyl acetylenedicarboxylates or dibenzoylacetylene with alkyl 2-nitroethanoates **42** in the presence of triphenylphosphine (Scheme 12).

Microwave-assisted multicomponent reactions are efficient and effective methods in the sustainable and diversity-oriented one-pot synthesis of heterocycles. Based on consecutive coupling-cycloaddition sequencing starting with room temperature coupling and subsequent dielectric heating for completion of the cycloaddition, Müller and coworkers [23], in 2008, reported on new avenues to the one-pot synthesis of isoxazole frameworks in a multicomponent reaction manner. Thus, the Sonogashira coupling of acid chloride **44** with terminal alkyne

45, followed by 1,3-dipolar cycloaddition under dielectric heating of *in situ* generated nitrile oxide from hydroximinoyl chloride **47** furnished isoxazole **48** in moderate to good yields (Scheme 13).

A dipolar cycloaddition strategy for the synthesis of substituted isoxazoles with complete regioselectivity at room temperature was developed by Grecian and Fokin in 2008 [24]. Thus, the cycloaddition reaction of nitrile oxides (generated *in situ* from hydroximoyl chlorides by treatment with Et_3N) and terminal or internal alkynes **15** in the presence of ruthenium(II)-catalyst affords 3,5-di- and 3,4,5-trisubstituted isoxazoles in excellent yields and with complete regioselectivity at room temperature (Scheme 14).

A first environmentally benign protocol using ionic liquid (IL) as noble solvent for the construction of the isoxazole ring was reported by the Valizadeh group in 2009 [25]. The novel method involves the reaction of β-diketone and hydroxylamine hydrochloride in IL [bmim]Br that provides biologically active isoxazoles in excellent isolated yields. The moderate reaction conditions, easy workup procedure, and recyclability of the nonvolatile IL make this protocol an environmentally friendly method amenable for scale-up synthesis (Scheme 15).
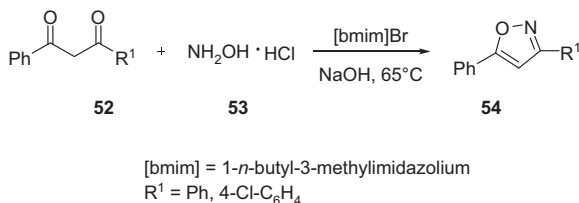
A versatile and efficient synthesis of a broad library of isoxazoles **58** was reported by Bhuniya and

Scheme 13

Scheme 14
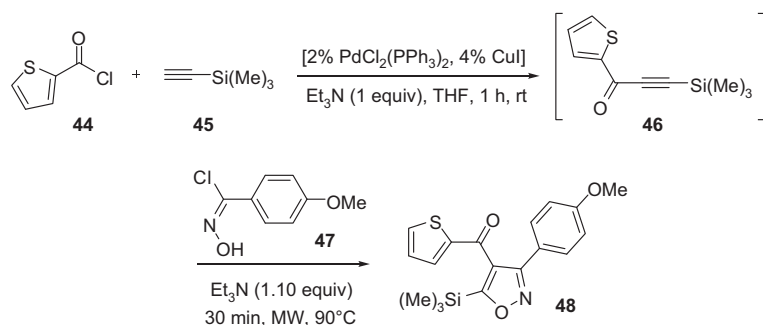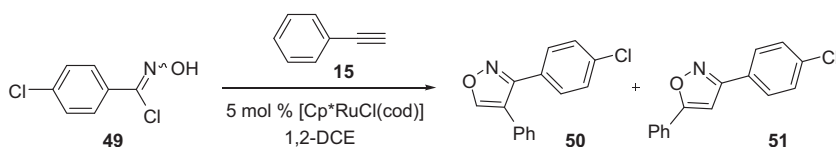
[bmim] = 1-*n*-butyl-3-methylimidazolium
R^1 = Ph, 4-Cl-C_6H_4

Scheme 15

coworkers in 2009 [26] via 1,3-dipolar cycloaddition (1,3-DC) of aldoximes **55** with dipolarophile **56** or **57** in the presence of Magtrieve™ (CrO_2), which is an efficient reagent for the oxidation of aldoximes to nitrile oxides, the intermediate products in this cycloaddition reaction (Scheme 16).

Campagne and coworkers [27] reported on an exquisite, efficient one-pot synthesis methodology for the

R^1 = Ph, 4-Cl-Ph   X = Ph, Bn, AcO, TMS

Scheme 16

Scheme 17

Scheme 18

construction of substituted isoxazoles **61**. Using *N*-sulfonyl-protected hydroxylamines **59** as binucleophiles, the propargylic substitutions catalyzed by iron allows the selective, *in situ* formation of propargylic oxime **60** from starting propargylic alcohols **58**. The substituted isoxazoles **61** are obtained in good isolated yields (Scheme 17).

A series of 3,4,5-trisubstituted isoxazoles exemplified by **64** were prepared by Chen and coworkers [28] in 2012 from *O*-methyl oxime substrates through a cascade process involving a Pd(II)-catalyzed 5-endo-dig cyclization to form the heteroaryl palladium intermediate, which is then transformed into another intermediate product after the loss of a methyl group. The Heck coupling between the last intermediate product and an alkene affords the trisubstituted isoxazole **64**. Electron-withdrawing substituents on the alkenes increase yields of the final products **64** (Scheme 18).

Dadiboyena and Nefzi [29] have developed an efficient parallel solid phase methodology to construct the diversity oriented substituted isoxazoles via 1,3-dipolar cycloaddition reaction. Thus, the cycloaddition of resin-bound alkenes or alkynes, synthesized from the corresponding resin-bound carboxylic acids, with *in situ* generated nitrile oxides, leads to the formation of the corresponding disubstituted isoxazoles (Scheme 19).

Very recently Suzuki et al. [30] developed a two-step protocol for efficient synthesis of highly functionalized polycyclic isoxazoles. The method involves 1,3-dipolar cycloaddition of stable benzonitrile oxides to *p*-quinone monoacetals **72** in a regioselective manner, favoring the formation of 4-acyl cycloadducts **73**, followed by MnO_2-mediated dehydrogenation to highly functionalized polycyclic isoxazoles **74** (Scheme 20).
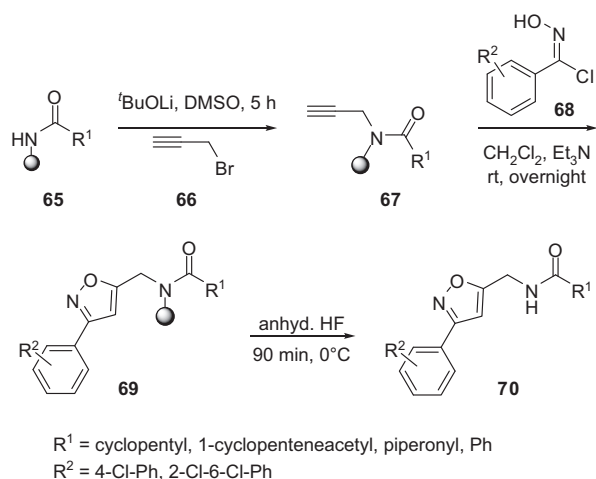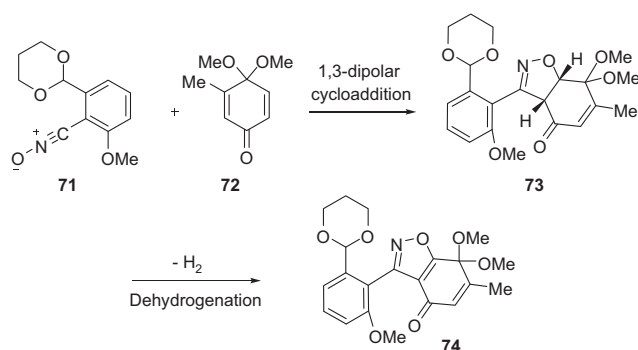
R^1 = cyclopentyl, 1-cyclopenteneacetyl, piperonyl, Ph
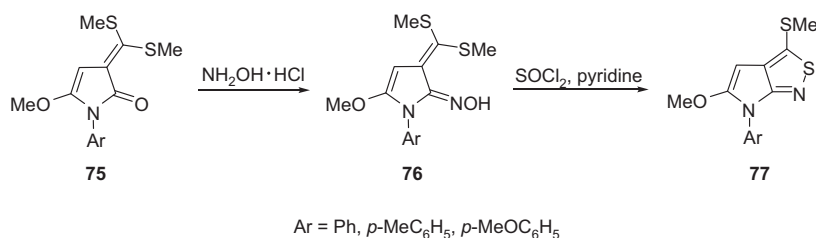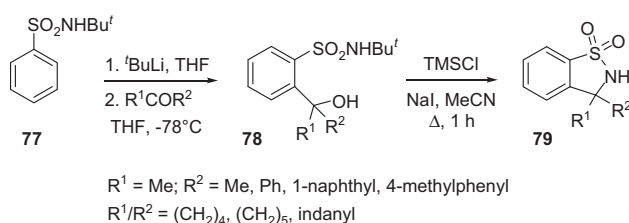R^2 = 4-Cl-Ph, 2-Cl-6-Cl-Ph
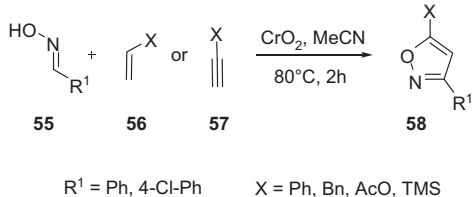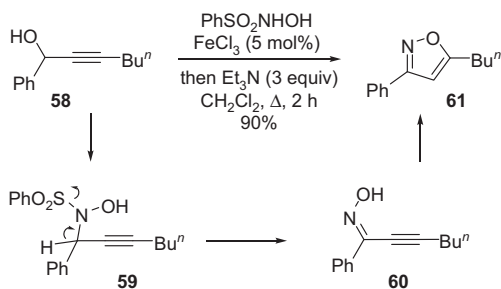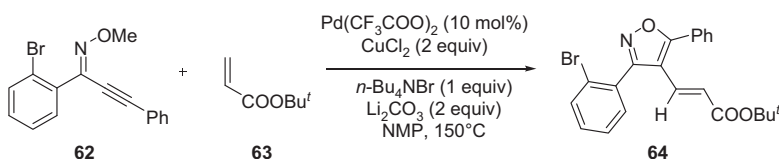
Scheme 19

Scheme 20

Isothiazoles

In 2002, Abd El-Nabi [31] reported on a methodology for the synthesis of highly substituted pyrrolo[2,3-*c*]isothiazoles. The method involves the treatment of 1-aryl-5-methoxy-pyrole-2-one with CS$_2$ followed by treatment with dimethyl sulfate in the presence of NaOH and dimethyl sulfoxide that gives 3-bis(methylsulfonyl)methylenepyrrol-2-one **75**. Compounds **75** are transformed into oximes **76** that are precursors to functionalized fused isothiazoles **77** (Scheme 21).

Ar = Ph, *p*-MeC$_6$H$_5$, *p*-MeOC$_6$H$_5$

Scheme 21

R^1 = Me; R^2 = Me, Ph, 1-naphthyl, 4-methylphenyl
R^1/R^2 = (CH$_2$)$_4$, (CH$_2$)$_5$, indanyl

Scheme 22

Shibata et al. [32] have developed a procedure for the synthesis of 3,3-disubstituted benzosultams **79** from benzenesulfonamide **77**. The regiospecific *o*-lithiation of *N-t*-butylbenzenesulfonamide **77** followed by reaction with ketones afforded the carbinol sulfonamides **78,** which underwent cyclization to the final products **79** (Scheme 22).

A facile synthesis of 3-substituted isothiazoles fused to a benzene ring has been developed by Devarie-Baez and Xian [33]. The protocol involves the nitrosation of *o*-mercaptoacylphenone **80** with isopentyl nitrite to form an unstable *S*-nitrosothio intermediate which undergoes an intramolecular aza-Wittig reaction to furnish the desired benzisothiazole **81 (**Scheme 23).

In 2011, the Shibasaki group [34] developed a distinct approach to enantio-enriched fused isothiazoles through a cascade of C-C and S-N bond formation reactions promoted by Cu catalysis. The unprecedented route involves a Cu-catalyzed asymmetric conjugate addition of allyl cyanide **83** to α,β-unsaturated thioamides **82** by soft Lewis acid/hard Brønsted base/hard Lewis base cooperative catalysis followed by Cu-catalyzed cascade cyclization to afford isothiazole **84** (Scheme 24).
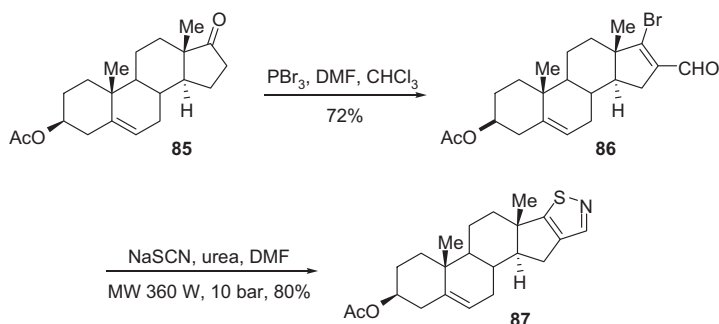
An efficient one-pot strategy for the synthesis of steroidal and non-steroidal isothiazoles found in some
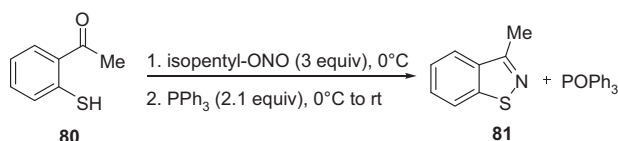
Scheme 23
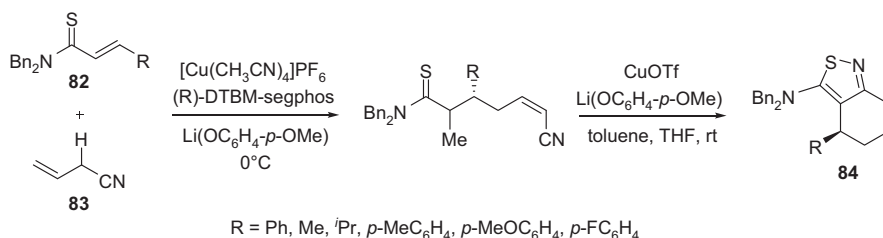
Scheme 24

Scheme 25

natural products and pharmaceuticals has been reported by Boruah et al. [35]. Thus, the reaction of ring annelated β-bromo-α,β-unsaturated aldehydes **86** with a mixture of sodium thiocyanate and urea as an environmentally benign source of ammonia under microwave irradiation (MWI) affords corresponding steroidal and non-steroidal isothiazole derivatives. These β-bromo-α,β-unsaturated aldehydes derivatives are efficiently synthesized from corresponding cyclic ketones **85** using the Vilsmeier formylation reaction (Scheme 25).

Conclusion

The past decade has seen a considerable expansion in research on the chemistry of 1,2-azoles due to numerous applications of these heterocyclic compounds in various fields such as medicine, agrochemistry, natural product synthesis, and catalysis. This review critically demonstrates the synthetic methodologies developed within the past 10 years for access to these heterocycles. Although the classical cyclocondensation methods are still the most commonly used procedures for their construction, new approaches need to be developed with the aim of increasing both yields and regioselectivities in the preparation of substituted 1,2-azoles. We hope that this review will be helpful to those who have a keen interest in the chemistry of 1,2-azoles.

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