ACCESS TO FIVE-MEMBERED *N*-HETEROAROMATIC COMPOUNDS: CURRENT APPROACH BASED ON MICROWAVE-ASSISTED SYNTHESIS

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Abstract. *N-Heterocyclic compounds (NHCs) have attracted significant attention in organic, industrial, and medicinal chemistry due to their recognized applicability in the development of biologically active compounds, coordination complexes, and functional materials. Specifically, five-membered N-heteroaromatic derivatives are essential due to their relevant structural and synthetic versatility derived from their exceptional electronic properties. As a result, different non-conventional techniques have been described to access diverse NHCs. In particular, the microwave-assisted organic synthesis (MAOS) is one the most widely used of these techniques due to proven and extensive applicability. In this respect and considering the relevance of NHCs and MAOS, this chapter highlights some recent works (2015 to 2021) on the synthesis of five-membered N-heteroaromatic compounds via MAOS, such as pyrroles, pyrazoles, imidazoles, and triazoles. As far as we know, this is the first contribution analyzing articles with the application of MAOS to prepare azole derivatives in a specific manner. These compounds are highly stable, and probably, this is the reason for the synthetic favorability of this family of NHCs by using reactions under heating with microwave irradiation.*

Contents

1. Introduction

N-Heterocyclic compounds (NHCs) play an essential role due to their excellent structural and synthetic versatility.[1-3] These compounds are classified according to the number of bonds and heteroatoms bearing the annular system, starting from three-member rings. However, heteroaromatic rings are usually the most relevant due to their electronic properties and ring-planar nature. These rings can have two types of nitrogen atoms, one pyridine-like (=N–) acting as an electron-pair donor center (like a base, nucleophile, or *N*-donor ligand) and the other pyrrole-like (–NR–) conferring a π-excedent character. Thus, five- and six-membered rings such as pyrroles, imidazoles, pyrazoles, triazoles, pyridines, and pyrimidines, are the more frequently studied derivatives due to their structural stability and diverse applicability. Likewise, various fused systems like indoles, benzimidazoles, indazoles, quinolines, carbazoles, purines, *etc.*, are included. In Figure 1, some relevant structures of *N*-heteroaromatic compounds are shown.[1-4]

Importantly, the *N*-heteroaromatic compounds present a wide range of biological, physical, and industrial applications.[1,3] A plethora of derivatives are used predominantly as pharmaceuticals and represent an essential part of medicinal chemistry because of their biological relevance; however, other applications vary from agrochemicals to copolymers.[5] Additionally, more recent research has highlighted the NHCs use

in photophysical or material science applications due to the previously mentioned electronic properties. For example, *N*-heteroaromatic compounds have been used to develop luminescent materials like Organic Light Emitting Diodes (OLEDs) or technological devices, synthesis of hybrid luminescent compounds and fluorescent molecular probes for diverse analytes sensing.[6-8] These scaffolds are often used for synthesizing other NHCs of larger size and complexity and are found in several natural and synthetic products. Indeed, most medicaments like antibiotics, antivirals, and anticancer drugs, have heteroaromatic rings (Figure 2).

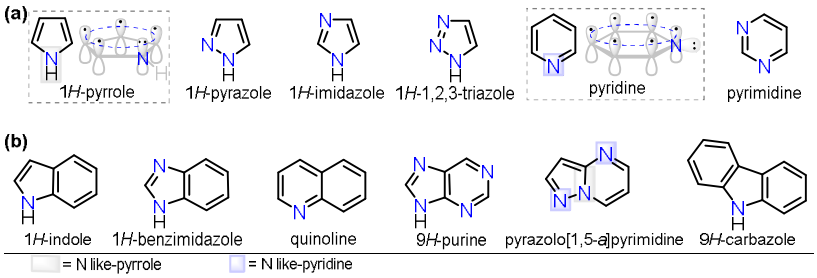


Figure 1. Structure of *N*-heteroaromatic compounds as (a) alone and (b) fused systems.

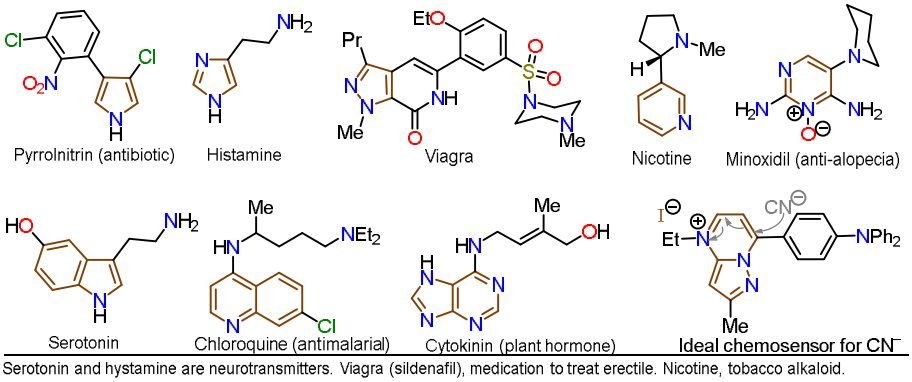


Figure 2. Examples of *N*-heteroaromatic (brown rings) compounds of general interest.

Importantly, *N*-heteroaromatic compounds have been obtained by numerous synthetic methodologies, collected and analyzed in several specialized contributions.[2,3,9] In the ring construction, synthetic methods mainly involve cyclization and some cycloaddition reactions. Aromatic substitution reactions are the usual procedures for later derivatizations, although some functionalized rings are obtained from the cyclization step. Moreover, post-functionalization reactions may become more relevant by allowing access to products with diverse applications. The classically employed syntheses to obtain the desired products are currently being replaced have had to be perfected or even superseded by novel approaches involving economic, efficient, selective, eco-compatible, and sustainable methods.[1-9]

Among the reported methods, microwave (MW) and ultrasound (US) are powerful tools for various chemical modifications with superior results regarding conventional techniques. Indeed, these are strategic tools to the synthesis currently carried out in our lab, and fortunately, we have the focused devices to develop them[8,10] (see Figure 3 below). These technologies have been used to synthesize several NHCs. Some syntheses use both tools; however, MW-assisted organic synthesis (MAOS) is the most widely used of these two techniques.[11] In this respect and considering the relevance of the NHCs, this chapter highlights some recent works (2015-2021) reporting the synthesis of five-membered *N*-heteroaromatic compounds *via* MAOS, and specifically: azoles like pyrroles, pyrazoles, imidazoles triazoles, and some fused rings 5:6. To the best of our knowledge, this is the first review highlighting articles with the application of MAOS to prepare azole derivatives in a specific manner, which are stable compounds.

In the last decades, electromagnetic radiation in the MW region has been widely used as an unconventional energy source to induce organic reactions. Starting from the first works on MAOS carried out by the groups of Gedye and Giguere in 1986 using domestic MW ovens, a plethora of articles have been published in this area. This technique is appreciated for inducing a wide range of organic reactions with various improvements compared to conventional heating methods such as short reaction times, purity of products by reducing unwanted side reactions, and decreasing the use of solvents that are often not required. In most of the reported works on MAOS, these benefits have been proven, and undoubtedly, the main advantage is the acceleration of the reaction due to the need for quick access, *via* simple transformations, towards numerous chemical products required today. Reactions of high synthetic utility like oxidations, reductions, alkylations, condensations, halogenations, etc., as well as the chemistry of heterocycles, fullerenes, polymers, peptides, carbohydrates, organometals, among others, have been carried out using this technology. As a result, essential applications in medicinal chemistry, drug discovery, and material sciences have been developed.[8-13]

Due to the MW-assisted organic synthesis advances, this technique has become routine for several laboratories worldwide. Consequently, there are various specialized instruments today, and with progress over the domestic ovens and those developed in the 90s, manly safety concern, reproducibility, and temperature and pressure control.[10-13] For example, Figure 3 shows the photographs we take of MW synthesis instruments in our lab, which are easy to use and allow carrying out reactions under open (Figures 3a and 3b), closed, solvent-free, pressurized conditions, and using an auto-sampler (Figure 3b).[8,10,14]

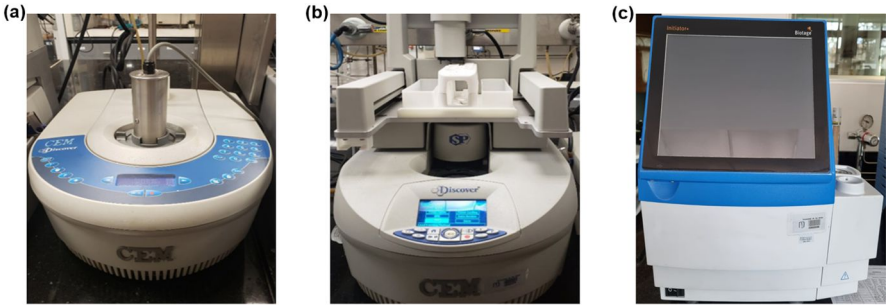


Figure 3. Photographs of MW synthesizers instruments in our lab. (a) CEM Discover, (b) CEM Discover SP® with auto-sampler, and (c) Biotage® Initiator+.

MW irradiation is located in frequencies from 0.3 to 30 GHz within the electromagnetic spectrum. Nevertheless, MW frequencies employed in organic synthesis vary between 2.45 GHz (low-frequency) and 5.5 GHz (high-frequency). Although the MW radiation has both an electrical and magnetic component, only the electric field (*E*) transfers energy as heat. To comprehend the role of MW radiation in inducing organic reactions, the physical rationale of this method must be addressed. These reactions are based on the heating generated within the reaction vessel *via* a speedy rotational motion that intensifies molecular collisions due to the direct interaction of radiation with organic molecules, drawing upon MW dielectric heating phenomena. Thus, MW absorption depends on the molecular polarity to favors rapid heat generation in the reaction mixture (Figure 4). This produced heat is then transferred to the reaction vessel by convection, while under conventional heating (Figure 4c), the reaction is induced with an external energy source that first heats the vessel (Figure 4d), reducing the energy transfer and the reaction rate.[8-14]

Importantly, there has been some debate on the exact motives why MW irradiation can favor chemical transformations, explicitly on whether effects are thermal Arrhenius-based or non-thermal due to stabilizing interaction of radiation with specific species in reactions. Several scientists had thought that was non-thermal MW effects. Nevertheless, the fact that a strictly thermal phenomenon favors MW chemistry in most cases is currently accepted. This process is due to the rapid heating, high reactions temperatures, and pressures achieved using MW dielectric heating in sealed vessels. The appliqued electromagnetic field has no direct influence on the reactions courses under MW irradiation.[12]

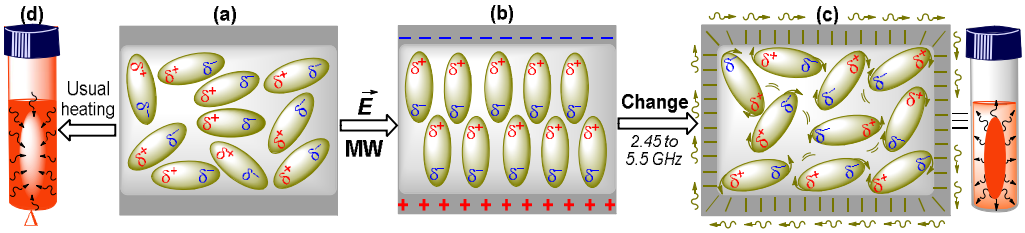


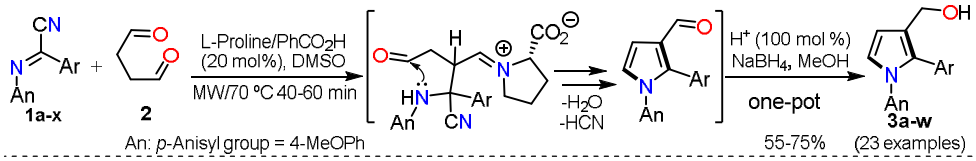
Figure 4. MW effect on dipolar molecules orientation. (a) Absence of *E* (*E*=0) and (b) presence of a static *E* (*E*≠0, ∂E/∂t=0) followed by (c) an alternating *E* (∂E/∂t≠0). (b) Conventional heating.

2. Pyrrole-based systems

The pyrrole ring constitutes a scaffold of various natural products, synthetically medicinal agents, and drug-like compounds. For example, pyrrole derivatives present various biological and pharmaceutical activities such as antibacterial, antiviral, antitumor, antioxidative, and anti-inflammatory. The synthesis of diversely substituted pyrroles has developed by interacting between different functional groups and using various reactions. These syntheses have promoted the creation of strategic pharmacophores in medicinal chemistry, conducting polymers for electronic devices, and π-extended pyrroles used in materials science.[15]

2.1. Pyrrole derivatives synthesis

Due to the wide range of applications that pyrrole derivatives present, several synthetic approaches have been described to their syntheses. Usual methods include Hantzsch, Barton-Zard, and Paal-Knorr reactions. Besides these methods, MAOS has been widely studied with outstanding results regarding the synthesis and functionalization of pyrrole derivatives. In this regard, five years ago, Kumar *et al.* reported a quick and highly efficient method for synthesizing substituted pyrrole-3-methanols **3a-w** from α-iminontriles **1** and succinaldehyde **2** under MW irradiation conditions. This approach consisted of a one-pot reaction involving an amine catalyzed direct Mannich reaction-cyclization-dehydrocyanation, followed by a reduction reaction with $NaBH_4$ to afford products in yields of up to 75% (Scheme 1).[16]



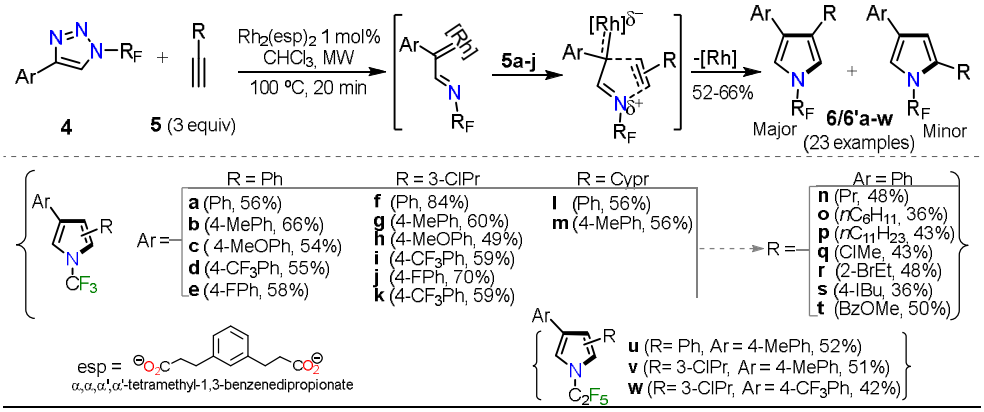
Ar = **a** (2-O_2NPh, 69%), **b** (3-O_2NPh, 72%), **c** (4-O_2NPh, 75%), **d** (2-ClNPh, 65%), **e** (3-ClPh, 70%), **f** (4-ClPh, 72%), **g** (2-FNPh, 63%), **h** (3-FPh, 65%), **i** (4-FPh, 73%), **j** (2-BrNPh, 60%), **k** (3-BrPh, 65%), **l** (4-BrPh, 73%), **m** (3-NCPh, 62%), **n** (4-NCPh, 70%), **o** (2,4-Cl_2Ph, 60%), **p** (3,4-Cl_2Ph, 63%), **q** (3-Br-4-FPh, 69%), **r** (2-Pyridyl, 65%), **s** (3-Pyridyl, 67%), **t** (4-Pyridyl, 68%), **u** (3,4-Cl_2Ph, 63%), **v** (3-Br-4-FPh, 69%), **w**(2-Pyridyl, 65%)

Scheme 1. MW-assisted synthesis of pyrrole-3-methanols **3a-w** *via* a strategy one-pot.

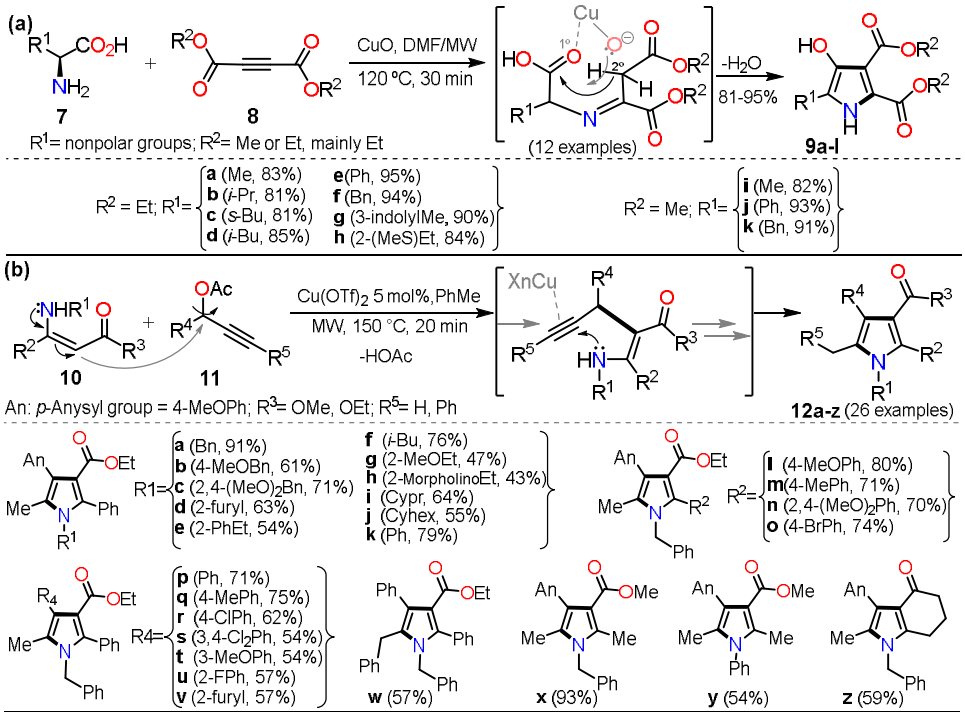
Beier and co-workers recently reported another significant example regarding annulation reactions towards pyrrole derivatives.[17] They synthesized a family of *N*-perfluoroalkyl-3,4-disubstituted pyrroles **6a-w** by rhodium-catalyzed *anti*-annulation of *N*-fluoroalkyl-1,2,3-triazoles **4** with several aromatic and aliphatic terminal alkynes **5**. Despite the promising results, products were isolated as regioisomeric mixtures of 1,2,4- and 1,3,4-trisubstituted pyrroles **6a-w** and **6'a-w**, respectively (Scheme 2).

The following example on the synthesis of pyrroles under MW consists of copper-promoted cyclization reactions. In this respect, Huang and co-workers reported a couple of years ago the synthesis of functionalized and tetra-substituted pyrroles **9a-k** *via* a tandem reaction under MW irradiation involving hydroamination and oxidative cyclization starting from amino acids **7** and dialkyl acetylenedicarboxylate **8** (Scheme 3a). Reactions proceed with high yields (81-95%) during 30 to 45 min, and copper oxide as catalyst. However, this synthetic method only works well by using amino acids substituted with fewer apolar

groups.[18] Likewise, MW irradiation from readily available β-enaminoesters **10** and propargyl acetates **11** to obtain substituted pyrroles **12a-z**, especially 3-phenylpyrroles (Scheme 3b).[19]



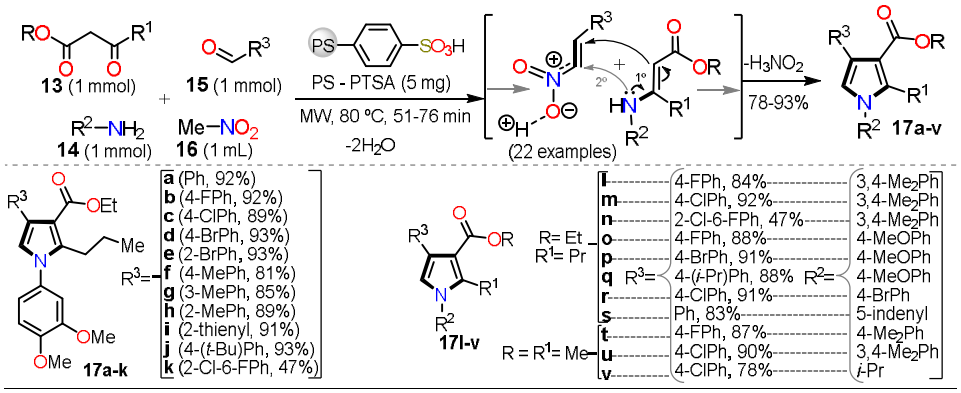
Scheme 2. MW-assisted synthesis of pyrroles from 1,2,3-triazoles *via* iminocarbenes of Rh.



Scheme 3. MW-assisted synthesis of a) tetra-substituted pyrroles **9a-k** from amino acids **7** and b) penta-substituted pyrroles **12a-z** from β-enaminoesters **10**.

On the other hand, Jeong and co-workers[20] described a solvent-free and MW-assisted four-component reaction for tetrasubstituted pyrrole derivatives synthesis **17a-v** using *p*-toluenesulfonic acid supported in polystirene (PS-PTSA) as a catalyst (Scheme 4). This environmentally benign one-pot approach, starting from β-ketoesters **13**, amines **14**, aldehydes **15**, and nitromethane **16**, led to the desired products with

excellent yields (78-93 %) by condensation/cyclo-condensation reactions, exhibiting several advantages like short reaction times, low cost, and easy workup procedure.



Scheme 4. MW-assisted synthesis of tetra-substituted pyrrole derivatives **17a-v** catalyzed by PS-PTSA.

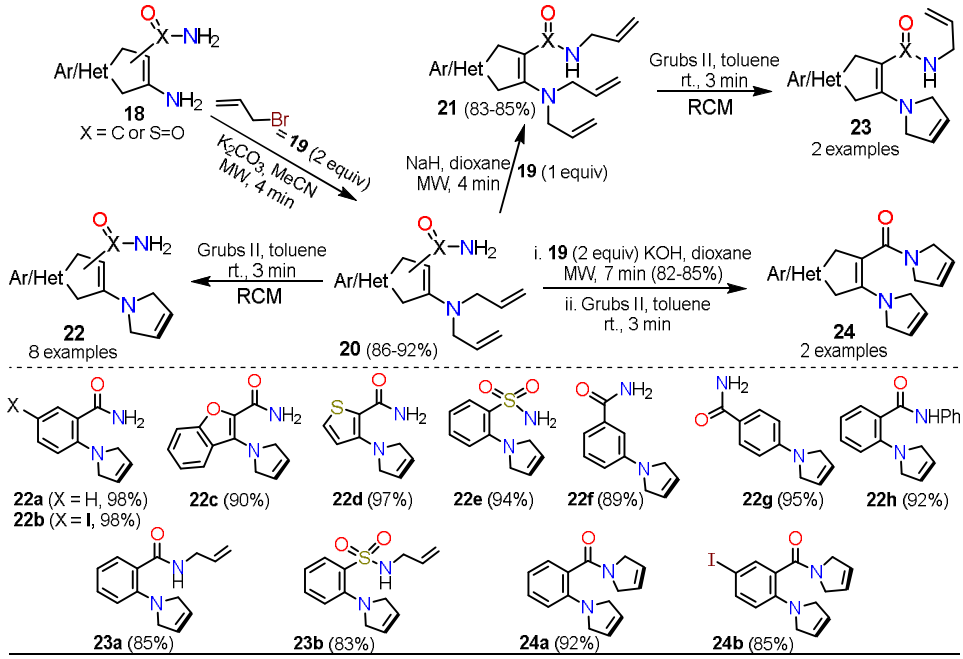
As the final example of pyrroles synthesis, we present the work reported by the Shanmugam's group. These investigators developed a diversity-oriented synthesis (DOS) strategy towards *N*-aryl- or *N*-hetaryl-pyrroles **22-24** containing an aminoamide fragment by a sequence of *N*-allylation followed by a ring-closing metathesis (RCM) process. The synthesis started with the MW-assisted reaction of 2-aminoamides **18** with allyl bromide **19** and proceeded by the respective di- **20**, tri- **21**, and tetra-allyl derivatives, substrates for the subsequent RCM. Pyrroles **22a-h**, **23a,b**, and **24a,b** were successfully obtained in high yields without any isomerization products (Scheme 5). This approach also allows the synthesis of pyridines and azepines by using homoallyl bromide as an alkylating agent, but herein, we only presented the synthesis of the pyrrole derivatives.[21]

Regarding a synthetic application on a pyrrole derivative, the synthesis of π-extended pyrroles allows studying the photophysical properties of these systems like solvatochromism. Last year, Ortega-Alfaro and co-workers described a family of push-pull biphenyl-azopyrroles **27a-i** obtained *via* a Suzuki cross-coupling reaction of 2-(4'-iodophenyl-azo)-*N*-methylpyrrole (or 3-(4'-iodophenyl-azo)-1,2,5-trimethylpyrrole) **25** with 4'-substituted phenylboronic acids **26** in excellent yields. Solvatochromic studies were carried out and concluded that the 4'-nitro-biphenyl backbone plays a key role in optimizing the photophysical properties of these azo compounds and exhibits a direct influence on their thermal isomerization kinetics (Scheme 6).[22]

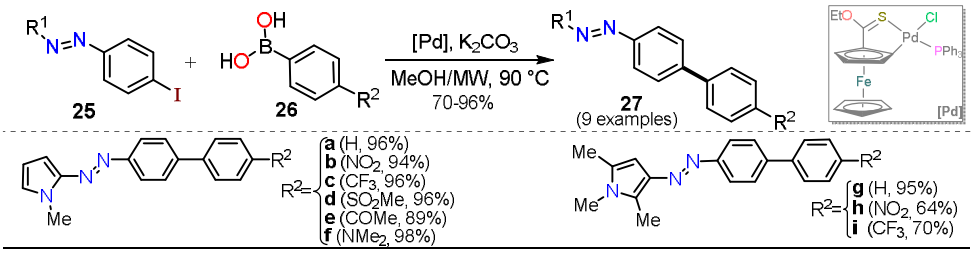
2.2. Aza-fused pyrroles 5:6

Aza-fused pyrroles to nitrogen six-membered rings (5:6 systems) are highly conjugated systems. They also present attractive properties and biological activities like antibacterial, antifungal, anti-inflammatory, antiepileptic, antidepressive, and antiviral agents. As a result, numerous synthetic strategies have been developed to obtain these scaffolds types. Some of these include oxidative and reductive cyclization, ring closure, multi-component coupling reactions, the cycloaddition of Schiff bases, and annulation reactions. By way of illustration, five years ago, Lee *et al.* established an innovative method for the synthesis of benzopyrimido[4',5':3,4]pyrrolo[2,1-*c*][1,4]oxazepines **33** and pyrimido[4',5':3,4]pyrrolo[1,2-a]quinoxalines **34** *via* the pyrrolo[3,4-*d*]pyrimidine-2,4(3*H*)-diones **31** and **32**, respectively. This method consisted firstly of adding the pyrrole ring under MW irradiation *via* intramolecular base-catalyzed cyclization between the 5-acetyl-6-(bromomethyl)pyrimidine **28** with *o*-aminophenylmethanol **29** or the *o*-phenylenediamine **30**. An atypical Pictet-Spengler reaction approach synthesized the target *N*-heteroaromatic products *via* an acid-catalyzed condensation with numerous aldehydes (Scheme 7).[23]

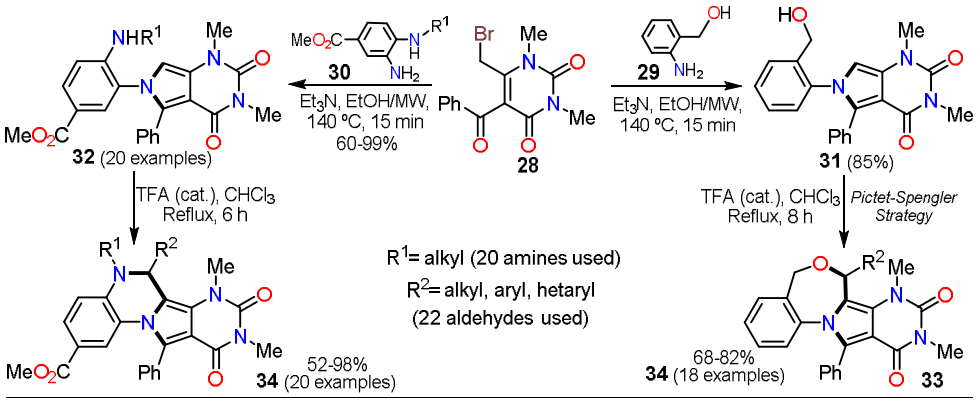
Reductive cyclization is an important method for obtaining aza-fused pyrroles. In this regard, selective cascade synthesis of alkyloxypyrrolo[1,2*a*]quinoxalinones **36** by a MW-assisted reductive cyclization from the methyl 1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxylate **35** was reported (Scheme 8).



Scheme 5. MW-assisted synthesis of *N*-aryl or *N*-hetarylpyrroles *via* *N*-allylation and RCM.

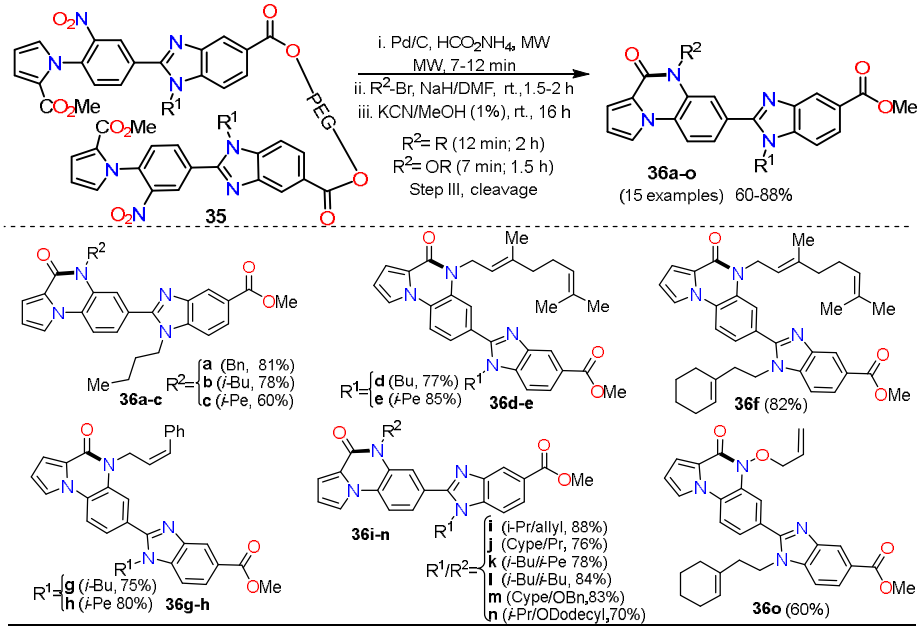


Scheme 6. Suzuki-Miyaura cross-coupling on pyrroles using different phenylboronic acids.



Scheme 7. Synthesis under MW of fused-pyrroles having 1,4-oxazepine **33** and quinoxaline **34** rings.

Products are substituted with a benzimidazole ring and were obtained in high yields (60-88%), and in addition, the reaction evidenced a broad scope. This synthetic approach constitutes the first description of *N*-hydroxypyrroloquinoxalinones using Pd/C with ammonium formate as reducing agents. Still, environmentally safe cyclization reactions can also be performed towards this scaffold.[24]



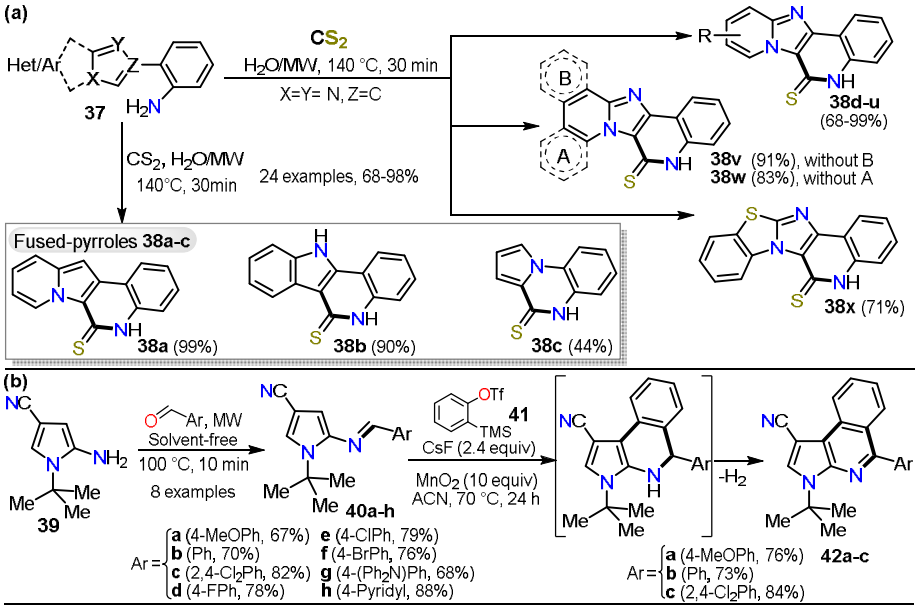
Scheme 8. MW-assisted synthesis of pyrrolo[1,2-*a*]quinoxalinones *via* reductive cyclization.

Recently, Wang *et al.* developed a MW-assisted reaction in aqueous medium to synthesize poly-heterocyclic-fused quinoline-2-thiones **38** by a 6π-electrocyclization strategy, starting from the aniline **37**, which is *ortho*-heteroaryl substituted (Scheme 9a). In addition to fused pyrroles **38a-c** of interest for this section, the investigators obtained a large family of fused imidazoles **38d-x** using the same approach. Remarkably, this synthetic methodology presents several advantages and is environmentally benign for it employs water as a solvent, presents shorter reaction times, and is metal- and additive-free.[25]

Considering that many of our works on heterocyclic compounds synthesis have been carried out by MW-assisted reactions, in 2019, we reported the efficient access towards pyrrolo[2,3-*c*]isoquinolines **42a-c** by an aza-Diels-Alder cycloaddition reaction of 2-arylideneaminopyrroles **40** with benzyne *in situ* generated from 2-(trimethylsilyl)phenyl triflate **41**.[15] The fused-pyrroles **42a-c** are substituted at position 5 with different electron-acceptor (A) or electron-donor (D) aryl groups. Aza-dienes **40a-h**, obtained by the MW-assisted solvent-free condensation reaction of 5-aminopyrrole **39** with arylaldehydes,[26] are essential substrates for this synthesis. Products **41** were obtained in high yields (73-84%), their photophysical properties were studied due to their high π-conjugation, and good Stokes shifts were found in different solvents. However, only **42c** showed high fluorescence intensity since its aryl group favors a twisted intramolecular charge transfer (TICT) effect. Suitable single crystals of aza-dienes and products were obtained for their study by single-crystal X-ray diffraction. The respective crystallographic and plenty supra-molecular analysis was conducted, and a remarkable structural connection between these studies with the synthetic and photophysical results was found (Scheme 9b).[15]

Another way to construct aza-fused pyrrole 5:6 scaffolds is by complexes catalyzed annulation reactions. Ellman *et al.* described the syntheses of pyrrolopyridazines **45a-s** starting from hydrazones **43** synthesized from *N*-aminopyrroles and aldehydes. Heterocyclic hydrazones **43** underwent Rh(III)-catalyzed dual C−H activation and coupling with aryl- and alkyl-substituted alkynes **44**, thus describing the annulation

reaction (Scheme 10a).[27] Finally, a base-promoted *anti*-annulation of enamines **46** and 2,3-epoxypropan-1-ones **47** is presented. Firstly, furanones derivatives (X=O in **46**) and **47** were heated under MW irradiation to produce furo[3,2-*b*]pyridines **48a-t** in good yields (56-82%). Subsequently, the *N*-aryl-4-aminopyrrol-2(5*H*)-ones (X=NH in **46**) bearing an electron-withdrawing group (EWG) favor obtaining pyrrolo[3,2-*b*]pyridines **49a-g** in moderate to good yields (48-82%). In contrast, their counterparts with an electron-neutral (ENG) or electron-donating group (EDG) underwent a different reaction pathway to form pyrrolo[3,2-*b*]pyrroles **50a-e** in good yields (62-76%) by C−C bond cleavage on a fragment of **47** (Scheme 10b).[28]



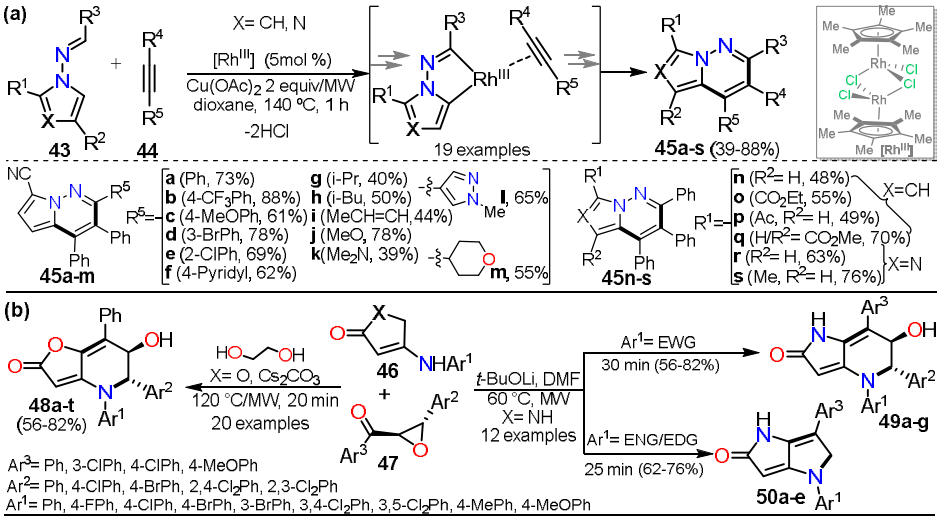
Scheme 9. Synthesis of aza-fused pyrroles 5:6 *via* a) cyclization reactions and b) cycloaddition.

3. Compounds incorporating the pyrazole ring

Pyrazole is a five-membered heteroaromatic ring with a planar structure bearing two nitrogen atoms at adjacent positions. Naturally occurring pyrazoles are scarce, but their synthesis and uses are essential in medicinal chemistry, technology, materials science, and industrial. The biological activities of pyrazoles include anti-inflammatory, sedative, antipyretic, analgesic, and antispasmodic action. These 1,2-diazoles are considered pluripotent ligands in coordination chemistry and are widely studied within the chemistry field because of the proven photophysical properties of compounds having the pyrazole ring.[29-31] For example, some pyrazole derivatives display large Stoke-shifts and blue luminescence, a tremendously important aspect in arousing OLED technologies. In the same way, those photophysical properties allow the pyrazole derivatives to be employed in different fields like optical brighteners, additives in detergents, UV-stabilizer for polystyrene, molecular probes development, and biological imaging applications.[7,29-32]

3.1. Pyrazoles synthesis

The pyrazole scaffold is found in several compounds that possess pharmaceutical and agrochemical applications. For this reason, its synthesis has been broadly described over the years. Classic methods for synthesizing the pyrazole-containing compounds include the cyclocondensation reactions between hydrazine derivatives with 1,3-bis-electrophilic compounds and [3+2] cycloaddition reaction between diazoalkenes (1,3-dipoles) and alkynes. Another common way towards pyrazoles synthesis consists of multi-component reactions (MCRs), in which the 1,3-bis-electrophilic reagent is *in situ* generated.[1,29,30]



Scheme 10. Synthesis under MW of a) pyrrolopyridazines **45a-s** and b) furopyridines **48a-t**, pyrrolopyridines **49a-g**, and pyrrolopyrroles **20a-e**.

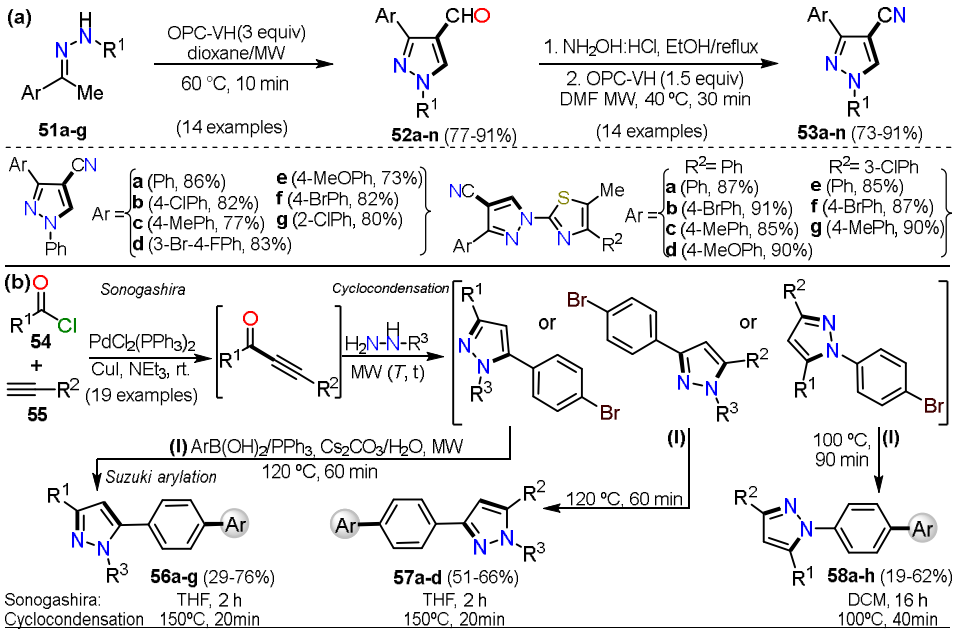
In the past few years, routes for access to pyrazole derivatives have been widely studied and modified to efficiently obtain pyrazole derivatives that present some of the aforementioned properties. Thereupon, some methods for the synthesis of pyrazoles will be described. Last year, Singh *et al.* developed an efficient way to obtention pyrazole-4-carbonitriles **53a-n** starting from hydrazone derivatives **51** and *via* the 3-ary4-formylpyrazole **52**. This synthetic method consisted of the condensation of pyrazole-4-carbaldehydes with hydroxylamine hydrochloride followed by reaction of the resulting oximes with the Vilsmeier-Haack (VH) reagent (prepared from *o*-phthaloyl dichloride (OPC) and DMF) under MW irradiation (Scheme 11a).[33,34] The synthesis afforded products with yields up to 91% and presented several advantages compared to classical versions like operational simplicity, avoiding toxic reagents and by-products, shorter reaction time, higher yields, and accessible workup procedures.[33]

Another method for synthesizing trisubstituted pyrazoles, specifically, rings bearing a bisaryl group (*in situ* generated from a 4-BrPh group) at position 1 for **56**, 3 for **57**, or 5 for **58**, was described *via* sequential palladium-catalyzed coupling-cyclocondensation-coupling (C^3) four-component synthesis, starting from acyl chlorides **54** and terminal alkynes **55**. This one-pot approach concatenates Sonogashira alkynylation and Suzuki arylation intercepted by pyrazole, forming *in situ* an intermediate ynone working as a 1,3-bis-electrophylic system in the cyclocondensations reaction with hydrazine derivatives (Scheme 11b).[35] This synthetic methodology allows the tailoring and optimization of the absorption and emission properties of the compounds herein obtained.

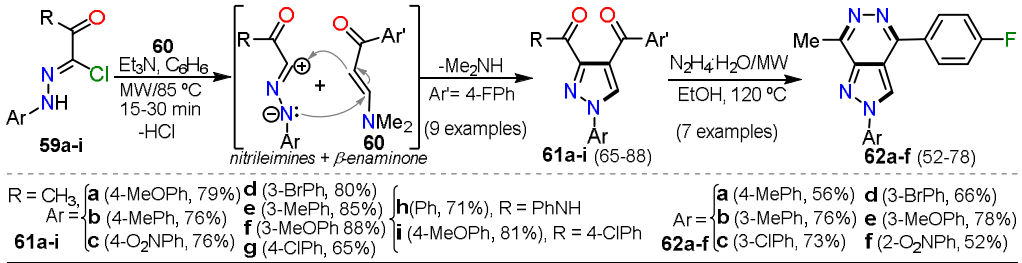
As mentioned previously, several methods for the regioselective obtention of pyrazole derivatives have been developed. In this respect, a facile and efficient synthetic methodology under MW irradiation towards novel pyrazole derivatives **61a-i** bearing a 4-fluotobenzoyl moiety was achieved four years ago by Althagafia and Shaaban. This synthesis proceeds in high yields (65-88%) *via* the 1,3-dipolar cycloaddition of nitrileimines (*in situ* generated from hydrazonoyl chloride **59a-i**) and the β-enaminones **60** in a regioselective manner. Notably, the MW-assisted reaction of **59** with hydrazine hydrate successfully afforded the fused-derivatives pyrazolo[3,4-*d*]pyridazine **62a-f** (Scheme 12). The authors highlight that compounds with fluorine atoms are utilized to obtain products with improved biological properties, and indeed, products obtained in this work were used for this purpose.[36]

Pyrazole derivatives may also present a considerable range of photophysical properties.[7,32] Two years ago, Garzón and Portilla developed innovative integrated *N*-(2-pyridyl)pyrazole-hemicyanine dyes **67a-e** for the colorimetric and ratiometric cyanide (CN^-) detection (Scheme 13a).[37] These dyes were obtained in overall yields up to 69% *via* a three-step sequence starting from acetophenones **63a-e**. This synthetic

approach proceeds *via* a formylation-cyclization-formylation sequence on hydrazones **64** under Vilsmeier-Haack conditions analogous to that presented in the synthesis of nitriles **53** (see Scheme 11a). The synthesis terminates with the Knoevenagel reaction between the 4-formylpyrazoles formed **65a-e** and the indolium salt **66**. Dyes are donor-π-acceptor (D-π-A) systems having indolium-salts conjugated with a modular donor group aryl/pyrazolyl. Photophysical results revealed that the dyes displayed high selectivity and sensitivity towards CN^- by interrupting the modular D-π-A structure by nucleophilic attack of CN^- on its iminium group ($C=N^+$). These chemodosimeters can be used for CN^- sensing without any additional special equipment since they change color from deep yellow to colorless with a naked eye.



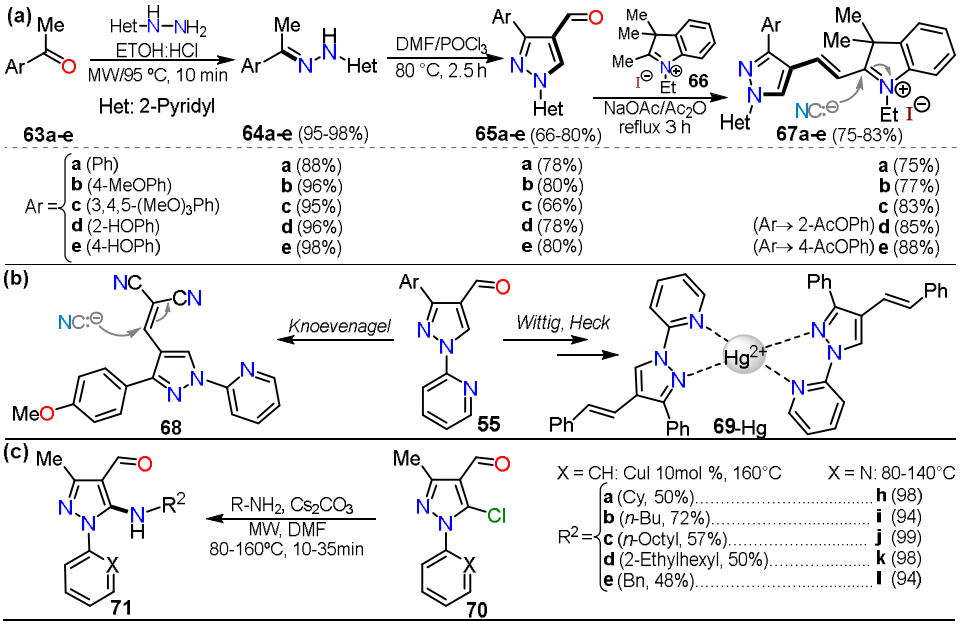
Scheme 11. Synthesis of a) pyrazole-4-carbonitriles **53a-n** and b) 1,3,5-substituted pyrazoles **56-58**.



Scheme 12. Synthesis under MW of pyrazole derivatives containing a 4-fluorophenyl group.

As an important annotation about molecular sensors synthesis, we have used 4-formylpyrazoles **65** to develop two other probes for detecting highly toxic ions like CN^- and Hg^{2+} in our lab, that is, compounds **68**[38] and **69**[39] (Scheme 13b). In the same line, Portilla and co-workers obtained 5-alkylaminopyrazoles **71** by an MW-assisted and Cs-mediate nucleophilic aromatic substitution (NAS) of primary alkylamine over the poorly activated 5-chloro-4-formylpyrazoles **70**.[40] Importantly, substrates **70** are badly reagents to the NAS reaction. Still, the reaction was carried out in short reaction times and moderate to excellent yields,

depending on the electronic nature of the aryl group on the pyrazolic core. In addition, under these reaction conditions, imine formation was not observed (Scheme 13c).



Scheme 13. a) MW-mediated synthesis of integrated *N*-(2-pyridyl)pyrazole-hemicyanine dyes **67a-e**. b) Probes for detecting CN^- and Hg^{2+}. c) Synthesis under MW of 5-alkylamino-1-arylpyrazoles **71**.

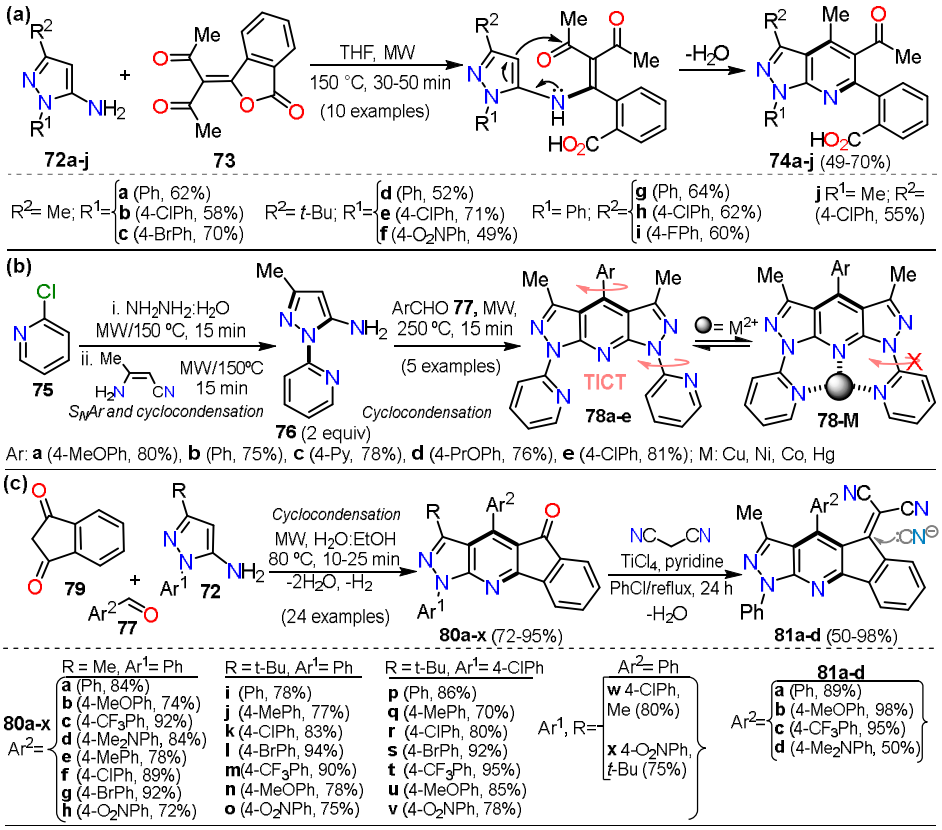
3.2. Some aza-fused rings 5:6

Fused 5:6 pyrazoles have also attracted much attention because they show interesting bioactivities like antipyretic, antibacterial, antitumor, antihistaminic, diuretic, antifolate, calcium-channel-antagonist, and anti-inflammatory activity. It has been found some of these derivatives can act as inhibitors of cyclin-dependent kinases, dihydrofolate reductase, and receptor and non-receptor tyrosine kinases.[9,29,30] In addition to their broad spectrum of bioactivities, fused NHCs have proven their usefulness in agricultural applications, technology, pigments, brightener additives, materials science, polymer science, among others.[7,32] This series of discoveries have directed the broad study of aza-fused 5:6 pyrazoles in medicinal chemistry, pharmaceutical, and industrial fields. Fused pyrazoles can also be utilized as molecular probes and functional organic fluorophores due to their wide range of optical properties and synthetic versatility. Classical methods for the obtention of this class of condensed systems concentrate on multistep syntheses terminating with cyclocondensations between aminopyrazoles and 1,3-bis-electrophilic reagents. Some synthetic ways will be detailed in this review regarding the MW-assisted synthesis of fused 5:6 pyrazoles, including rings like pyrazolo[3,4-*b*]pyridines, pyrazolo[1,5-*a*]pyrimidines, and others fused pyrazoles.[1,9,29,30]

Concerning pyrazolo[3,4-*b*]pyridines synthesis, four years ago, Portilla and co-workers described the synthesis of fully functionalized pyrazolo[3,4-*b*]pyridines **74** *via* isobenzofuranone ring-opening of the substrate **73** under MW irradiation. The regioselective reaction between 5-aminopyrazoles **72** and 3-(3-oxo-2-benzofuran-1(3*H*)-ylidene)pentane-2,4-dione **73** to provide **74**, proceeded by a domino aza-Michael-cyclization-dehydration sequence. Notably, the authors were able to isolate the pyrazolyl-enamine intermediate, clarifying the reaction mechanism involved with the exciting heterocyclic 1,3-biselectrophile **73** (Scheme 14a).[41]

Two years later, a work was published by the same group regarding the synthesis of another derivative of pyrazolo[3,4-*b*]pyridine; specifically, fluorescent 1,7-dipyridyl-bis-pyrazolo[3,4-*b*:4′,3′-*e*]pyridines **78a-e**. These compounds were used as turn-off reversible chemosensors for nanomolar detection of Cu^{2+}, Co^{2+},

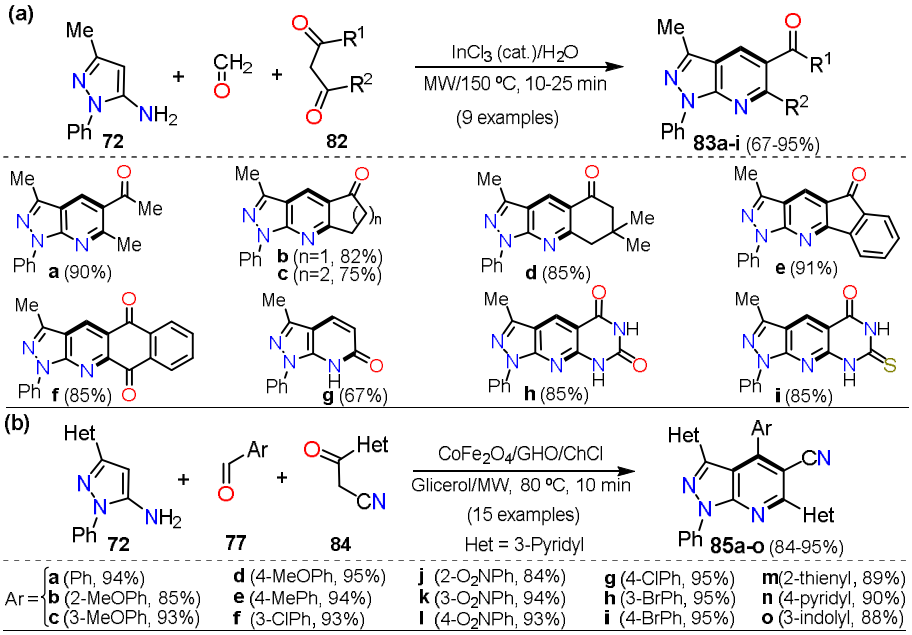
Ni^{2+}, and Hg^{2+}, based on a TICT fluorescence mechanism *via* complexes **78-M** (Scheme 14b). The synthesis proceeded by a three-step sequence starting from 2-chloropyridine **75**. Desired products were obtained in up to 63 % yields by a pseudo-three-component reaction between 2 equiv of 5-amino-1-(2-pyridyl)pyrazole **76** and 1 equiv. of arylaldehydes **77**.[42] In a similar manner, Orrego-Hernández *et al.* reported the synthesis of other pyrazolo[3,4-*b*]pyridine derivatives **80a-x**, but in this case, fused to an indene ring forming a 4-azafluorenone system. Indeno[1,2-*b*]pyrazolo[4,3-*e*]pyridines **80a-x** were obtained by MCR of arylaldehydes **77**, indan-1,3-dione **79**, and 5-aminopyrazoles **72**. The 4-azafluorenonas were later used as precursors of novel dicyanovinylidene derivatives **81a-d** containing different acceptor or donor aryl groups at position 4 (Scheme 14c). Compounds **81** were preliminarily studied for detecting CN^-, and photophysical and computational studies concluded that they are intramolecular charge transfer (ICT) fluorophores.[43]



Scheme 14. MW-assisted synthesis of pyrazolo[3,4-*b*]pyridines a) **74**, b) **78**, and c) **81**.

In general, MCR to obtain pyrazolo[3,4-*b*]pyridines proceed by *in situ* formation of the 1,3-bis-electrophilic reagent, usually based on the condensation reaction of an active methylene compound with an aldehyde molecule.[42,43] Some other investigation groups have worked on this method; for instance, Polo *et al.* reported the MW-assisted three-component reaction of 5-amino-1-phenyl-3-methylpyrazole **72a**, formaldehyde, and 1,3-diketones **82** in water using $InCl_3$ as catalyst (Scheme 15a). The reaction proceeds in high yields (67-95%), allowing access to different pyrazolo[3,4-*b*]pyridines **83a-i**.[44] Similarly, Zhang and co-workers synthesized 1,3,4,6-tetra-aryl-5-cyanopyrazolo[3,4-*b*]pyridines **85a-o** by the MCR under MW irradiation between 5-aminopyrazole **72**, hetaroylacetonitrile **84**, and arylaldehydes **77** in choline chloride

(ChCl)/glycerol (Scheme 15b). For this study, sulfonic acid nanoparticles anchored by graphene oxide (G) work as a catalyst system, allowing high yields (84-95%) in products.[45]



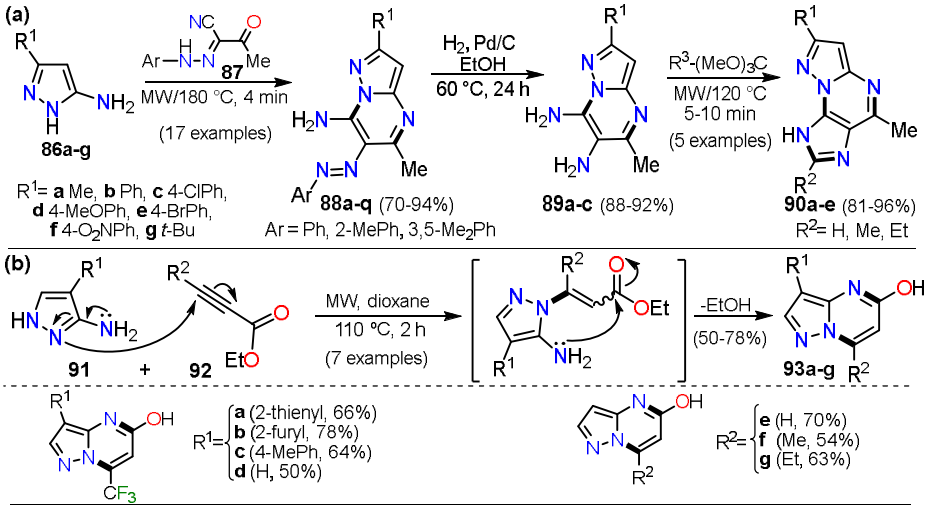
Scheme 15. Three-component synthesis under MW of pyrazolo[3,4-*b*]pyridines a) **83** and b) **85**.

It is important to note that if 5-aminopyrazoles unsubstituted at the ring nitrogen atom are used in the pyrazolo[3,4-*b*]pyridines ring construction, the pyrazolo[1,5-*a*]pyridine heterocyclic core formation is mainly observed. This result is evidenced even when the synthetic transformation occurs through enones (that is, carbonyl compounds α,β-unsaturated) as bis-electrophilic systems that are substrates favoring the formation of pyrazolo[3,4-*b*]pyridines.[41-45] This heterocyclic core is a privileged scaffold towards designing several derivatives with relevant biological and physical uses because of its proven and functional synthetic versatility, which favors structural modifications throughout its periphery.[9,29] Physical applications of this molecular motif are of current value; for example, applications in materials sciences[9,46] and a great tendency to form crystals with important supramolecular properties towards applications in the solid-state have been found.[46-48] Therefore, various reviews related to the synthesis of this structural motif have been described in the literature,[9] and indeed, more of our recent works are pyrazolo[1,5-*a*]pyrimidine derivatives-based.

In this context, Castillo *et al.* developed a MW-assisted solvent-free method for the regioselective synthesis of 6-(aryldiazenyl)pyrazolo[1,5-*a*]pyrimidines **88a-e** through the cyclocondensation reaction of 3-oxo-2-(2-arylhydrazinylidene)butanenitriles **86** with 5-amino-1*H*-pyrazoles **87**.[49] This synthetic approach allowed the convenient use of compounds **88** as strategic intermediates for synthesizing pyrazole[5,1-*b*]purines **90** *via* a complete cyclization-reduction-cyclization sequence from the reagents **86** and **87** (Scheme 16a). This sequence implicated the key and efficient conversion of **88** to their corresponding pyrazolo[1,5-*a*]pyrimidine-6,7-diamines **89** by a Pd-catalyzed reductive azo cleavage, which cyclized with orthoesters provided the tricyclic products **90** in excellent overall yields (60-70%).

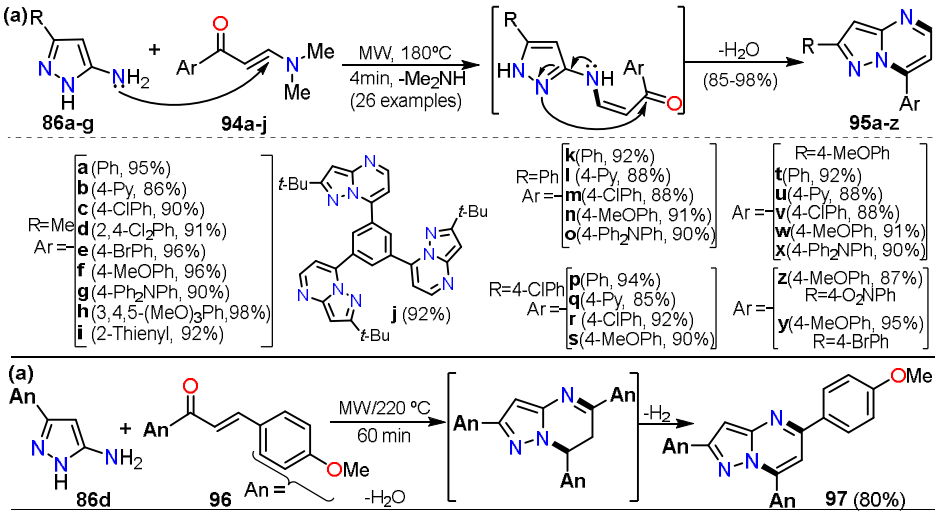
On the other hand, the employment of 1,3-biselectrophilic ynones that allow access to pyrazolo[1,5-*a*]pyrimidines derivatives has been a matter of interest for different investigators; for example, Jismy *et al.* applied this kind of approach with excellent results.[50,51] Specifically, the authors used a MW-assisted reaction between 5-amino-1*H*-pyrazoles **91** and ethyl ynoates **92**, which affords 5-hydroxy substituted products **93a-g** in moderate to good yields (Scheme 16b).[51] This investigation evaluated different

conditions like temperature and reaction time, solvent, Lewis acid catalysis, and heating under MW irradiation. Notably, products **93a-d** are substituted at position 7 with the group CF_3 as a relevant bioisostere, which could be added in this simple manner, avoiding complex post-functionalization reaction steps.[50,51]



Scheme 16. Synthesis of a) pyrazolo[5,1-*b*]purines **90** and b) 5-hydroxypyrazolo[1,5-*a*]pyrimidines **93**.

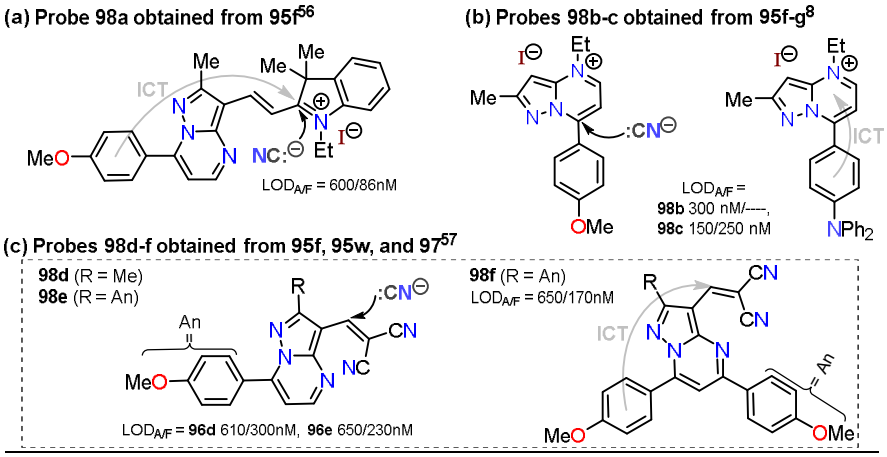
As an important observation, the β-enaminone fragment use as a 1,3-biselectrophilic system favors the reactivity towards *NH*-aminopyrazoles and, as a result, the reaction performance in respect to other 1,3-bis-electrophilic compounds. Our research group has been working hard on this issue both in the synthetic field by using MAOS[52,53] and developing functional fluorophores (Scheme 17),[46,53,54] which has allowed us to obtain molecular probes to detect a highly toxic ion like CN^- *via* nucleophilic addition reactions on receptor EWGs and ICT photophysical phenomena (see Scheme 18, probes **98a-f**).[8,55,56]



Scheme 17. a) Synthesis under MW of pyrazolo[1,5-*a*]pyrimidines a) **95a-z** and b) **97**.

Through these investigations, we synthesized a large family of pyrazolo[1,5-*a*]pyrimidines **95a-z** in a regioselective manner and high yields (85-98%) using different β-enaminones **94**, also prepared under MW irradiation, and aminopyrazoles **86a-g**.[46,52-54] The reaction curse is favored with the dimethylamino leaving group on the substrate *via* an initial addition-elimination process aza-Michael type, using the amine (NH_2) group of **86** and the Cβ of **94** (Scheme 17a).[8,46,52-56] This reaction is often complicated when simple enones like chalcone derivatives are used because of the unsaturation required in products, 1,3-bis-electrophilic substrates bearing a leaving group at β-position are necessary. However, by using chalcones is possible to obtain products 5,7-diarylsubstituted from substrates available by a simple process like the Claisen-Schmidt reaction. Recently, we developed the synthesis of 2,5,7-tris(4-methoxyphenyl)pyrazolo[1,5-*a*]pyrimidine **97** starting from (*E*)-1,3-bis(4-methoxyphenyl)prop-2-en-1-one (chalcone **97**) and aminopyrazole **86d** under MW irradiation (Scheme 17b). This reaction proceeds under reaction conditions relatively strong (high temperature for a relatively long time) due to the poor reactivity of **96**.[56]

Notably, pyrazolo[1,5-*a*]pyrimidines **95f**, **95g**, **95w**, and **97** (Scheme 17) were successfully used as precursors to obtain the six molecular probes **98a-f** for detecting CN^- with exceptional detection limits (LODs) and also using MAOS in some later reactions. These probes work by nucleophilic addition reactions on different receptor fragments such as indolium salt **98a**,[55] pyrimidinium salt,[8] and dicyanovinylidene[56] (Scheme 18a). Notably, in our more recent and prominent example, we developed two new probes based on the 7-arylpyrazolo[1,5-*a*]pyrimidinium salts **98b** and **98c**, using a sustainable and applicable method in CN^- sensors synthesis. Compound **98c** was an ideal probe with improved photophysical properties because its triphenylamine (TPA) group improved the ICT process. This ideal probe detected CN^- in EtOH/H_2O 4:1 with high selectivity and sensitivity by three spectroscopic channels, LOD=150 nM (Abs/327 nm), 150 nM (Abs/478 nm), and 250 nM (Flu/447 nm). Additionally, probe **98c** is a reversible chemosensor in the presence of silver ions (Ag^+ from $AgNO_3$) by four consecutive titrations with the analyte (Scheme 18b).[8]



Scheme 18. Probes for cyanide bearing a) indolium salt, b) dicyanovinylidene, and c) pyrimidinium salt.

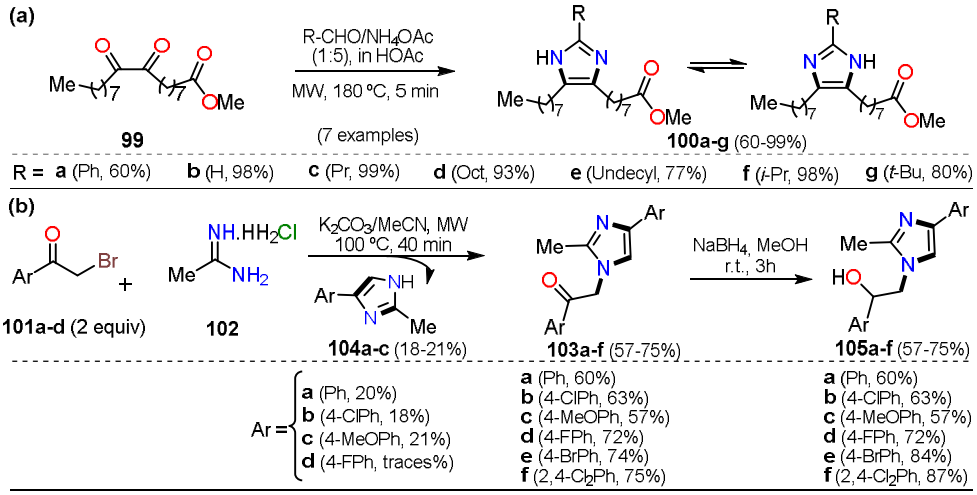
4. Imidazole derivatives

Imidazole (1,3-diazole), like pyrazole (1,2-diazole), is a heteroaromatic ring containing two heteroatoms and analogs structural properties; however, imidazole is electron-richer than pyrazole due to the nitrogen atoms positions.[1-3] Imidazoles have been an object of interest in the past decades because it exhibits many biological properties such as anti-inflammatory, antiviral, antimicrobial, antifungal, and antitumoral activities.[1,57-59] Imidazoles also act as inhibitors of p38 MAP kinase[60] and are present in molecular probes development.[61] Aside from the biologically relevant properties that several imidazole derivatives present, the 1,2-diazolic core is also a subject of intense study in organic synthesis. Imidazoles can be found in ionic liquids, *N*-heterocyclic carbenes, and act as organocatalysts or ligands for organometallic complexes.[60,62]

4.1. Imidazoles synthesis

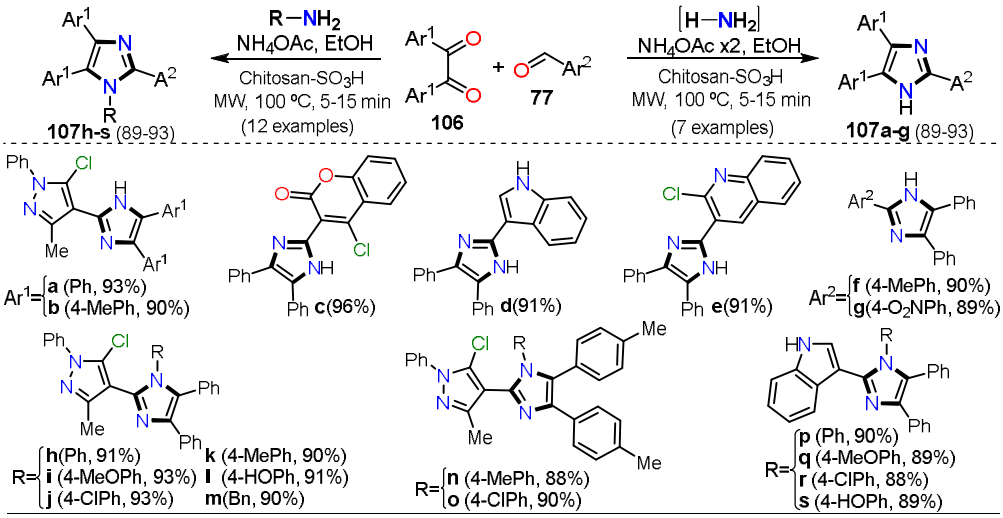
Due to its remarkable properties and broad applications, syntheses of the imidazole scaffold have been widely described. Syntheses based on catalysts, MCR, assisted by MWs, and the classic methods of (i) Debus-Radziszewski and (ii) Bredereck have been carried out. Method (i) is based on the interaction of α-dicarbonyl compounds with amines (or NH_3) and aldehydes, while α-hydroxyketones with formamide are used in (ii).[1,57-62] There are also some significant synthetic variants, like the use of α-haloketones and amidines.[63] However, all these syntheses form two new C-N bonds, specifically with the carbon atoms in the 4 and 5 positions. In 2021, the Debus-Radziszewski synthesis of the imidazoles **100** starting from the fatty 1,2-diketone **99**, aldehydes, and ammonium acetate was reported. A variation of this approach replaces ammonia with primaries amines and affords *N*-substituted imidazoles. Several catalytic ways like organocatalysts, ionic liquids, Brønsted acids, Lewis acids (some solid-supported), and metal oxides are described to promote the reaction. However, the work herein presented constitutes a catalyst-free, MW-assisted synthesis of 2,3,5-trisubstituted imidazoles **100** with yields up to 99 % (Scheme 19a).

In 2018, Elejalde *et al.* carried out the regioselective synthesis and *in vitro* antifungal evaluation of *N*-phenacyl-4-aryl-2-methylimidazoles **103** using the synthetic variant starting from α-haloketones and amidines.[59,63,64] They obtained products *via* the *pseudo*-three-component reaction of α-bromoacetophenones **101** with acetamidine hydrochloride **102** in acetonitrile and K_2CO_3 as a base. The reduction of the carbonyl group in **103** offered the respective alcohols **105** in high yields (70-85%), which have the privileged fragment 2-hydroxyethyl present in various antifungal azoles.[63,64] The formation of **103** proceeded with good yields (57-72%) *via* an MW-assisted one-pot sequence. However, according to the few reports of analogous synthesis, the reaction also allowed to isolate the expected 1*H*-imidazoles **104** as minor products (18-21%).[59] Products **103** to **105** were tested for antifungal activity against two clinically important fungi, *Candida albicans* and *Cryptococcus neoformans* showing promising results. Additionally, structures of three types of compounds were confirmed by single-crystal X-ray diffraction (Scheme 19b).[59,63,64]



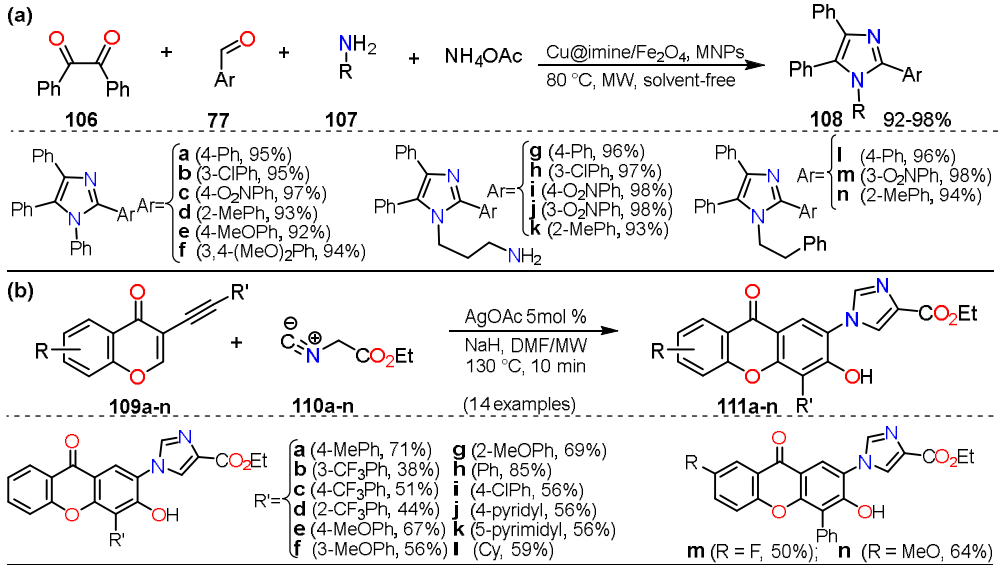
Scheme 19. Synthesis under MW irradiation of trisubstituted imidazoles a) **100** and b) **103**.

As mentioned above, imidazole synthesis is characterized by the presence of a catalyst. Last year, Siddiqui and Khan developed an efficient synthetic method of tri- and tetrasubstituted imidazoles **107a-s** from α-diketones (benzil derivatives) **106** using functionalized chitosan as a biodegradable solid acid catalyst. [65] This one-pot four-component synthesis of products **107a-s** using the 1,3-bis-electrophile **106**, arylaldehydes **77**, ammonia derivatives, and ammonium acetate in the presence of biodegradable and highly efficient catalyst chitosan-SO_3H proved to be an environmentally safe, simple, and highly efficient methodology for access to highly substituted imidazoles (Scheme 20).[65]



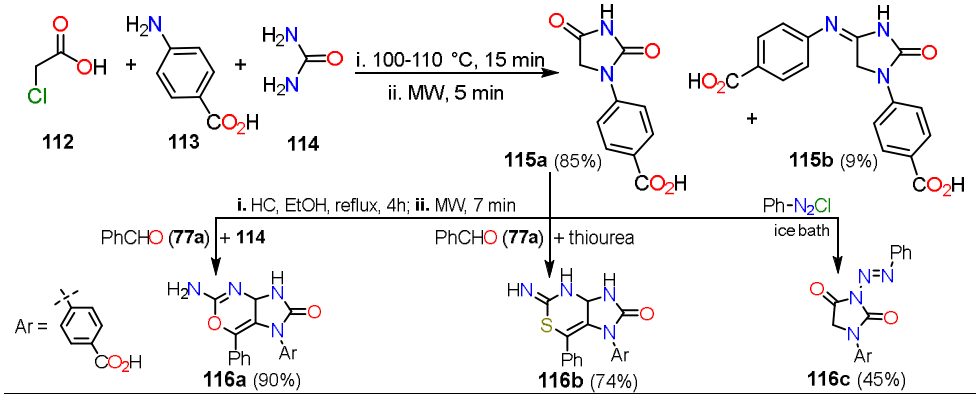
Scheme 20. Synthesis of tri- and tetrasubstituted imidazoles **107a-g** and **107h-s**, respectively.

Another green approach for synthesizing 1,2,4,5-tetrasubstituted imidazoles **109** from benzil **106**, arylaldehydes **77**, primary amines **108a-n**, and ammonium acetate, was reported by Thwin *et al.* in 2019.[66] This innovative synthetic method is based using Cu@imine/Fe_3O_4 Magnetic Nanoparticles (MNPs) as a recyclable catalyst under solvent-free conditions and MW irradiation (Scheme 21a). A much similar reaction was reported by Esmaeilpour *et al.*[67] in 2015, employing Fe_3O_4@SiO_2-imid-PMAn magnetic porous nanosphere as the recyclable catalyst. Ultimately, a base as NaH promoted the one-pot tandem reactions of 3-(1-alkynyl)chromones to form 2-nitrogen-substituted xanthones **111a-n** were reported.[68] The reaction consisted of a silver-catalyzed dimerization of ethyl isocyanoacetates **110** that triggered the tandem reaction of 3-(1-alkynyl)chromones **109** in a one-pot way to afford novel substituted xanthones (Scheme 21b).



Scheme 21. MW-assisted catalyzed reactions for the synthesis of imidazoles derivatives a) **108** and b) **111**.

According to the advantages of the α-halocarbonyls compound as 1,2-biselectrophilic substrates in imidazoles synthesis *via* cyclocondensation reactions with urea analogs (urea, thiourea, amidines *etc.*),[63] Selim and El-Azim[69] developed a method to prepare of an imidazole derivative starting from chloroacetic acid **112**. The authors synthesized 4-(2,4-dioxoimidazolidin-1-yl)benzoic acid **115a** in high yield (85%) *via* a MW-assisted one-pot reaction between **112**, 4-aminobenzoic acid **113**, and urea **114** under solvent-free conditions; however, the reaction also provides the imidazole derivative **115b** as a by-product (9% yield). Moreover, **115a** was successfully used in the synthesis of some fused derivatives. For example, the cyclocondensation reaction between the imidazole derivative **115a**, benzaldehyde **77a**, and urea or thiourea formed the respective fused imidazoles **116a** or **116b** in high yields. Moreover, the reaction of **115** with benzenediazonium chloride delivered the *N*-phenyldiazenylimidazolone **116c** (Scheme 22).



Scheme 22. MW-assisted synthesis of imidazole derivatives *via* cyclocondensation reactions.

4.2. Aza-fused imidazoles 5:6

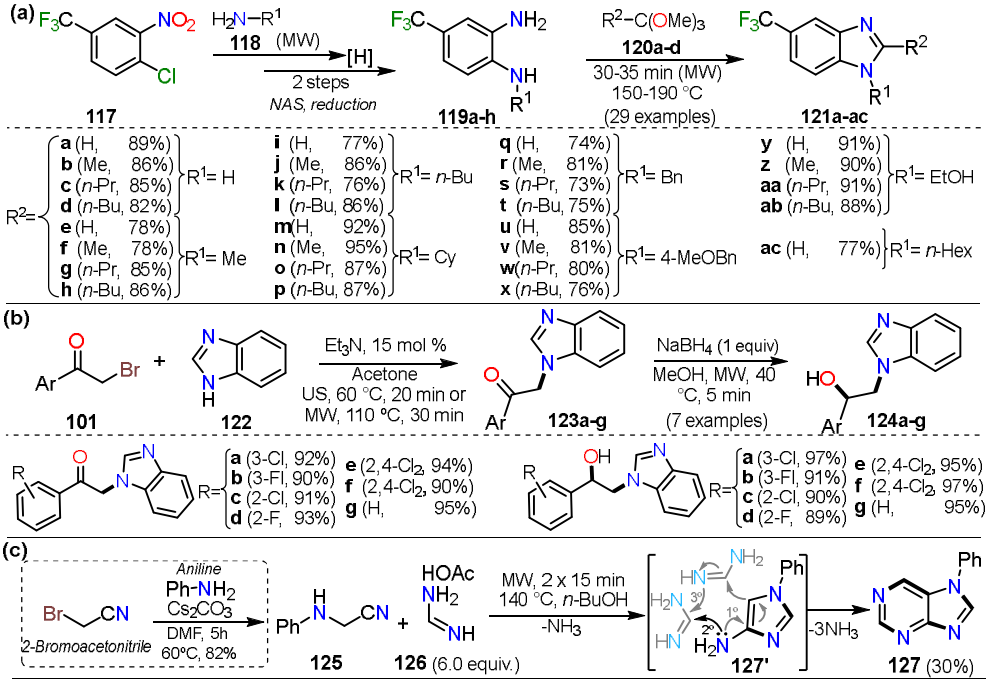
Aza-fused 5:6 imidazoles also present biological properties as their free analogs, making these scaffolds of great interest in the medicinal and pharmaceutical fields.[49,70] Some of these properties include antifungal, antibacterial, antiviral, anticancer, and antiepileptic activity. In addition, compounds containing the aza-fused 5:6 imidazole core can act as cardiac stimulating agents and uterine relaxants.[71] Despite all these biological activities, aza-fused 5:6 imidazoles also exhibit numerous photophysical properties. Because of this wide range of applications, several synthetic methods have been described for the obtention of these moieties. Some of these methods encompass cyclocondensations, oxidative couplings, tandem reactions, amino-oxygenations, and hydroamination reactions.[71] It is crucial to note that purine derivatives are the most prominent NHCs;[49] however, despite the benzimidazole is a fused 5:6 imidazoles that does not have nitrogen atoms in its 6-membered ring, the effectiveness of this scaffold has been demonstrated in several clinically critical therapeutic areas as well other different areas of science in general.[1,72-74] Consequently, a couple of examples of MW-mediated synthesis of imidazole derivatives are also discussed in this section.

Apart from purines,[49] others of the most common examples of aza-fuse 5:6 imidazoles are the [1,2-*a*] condensed system. The most traditional approach to obtain this type of fused heteroaromatic compounds is through the condensation of α-haloketones with 2-aminopyridines (or 2-aminopyrimidines[70]) with or without catalysis, the same way as to get their free analogs.[70,71] However, conventional syntheses of imidazo[1,2-*a*] heterocycles often require high temperatures and long reaction times. Replacing oil baths with MW reactors cascade reactions to take place in the same reaction vessel, thus shortening reaction times, reducing the generation of waste chemicals, and the yields under much cleaner reaction conditions.[1,75,76] Hereunder, some synthetic approaches for the obtention of benzimidazoles and aza-fused 5:6 imidazoles will be described.

Four years ago, Portilla and co-workers reported a quick and efficient synthetic approach towards a family of 1,2-dialkyl-5-trifluoromethylbenzimidazoles (29 compounds **121a-ac** in up to 83% overall yield) by a three-step synthesis sequence (NAS, reduction, and cyclocondensation reactions) starting from 1-chloro-2-nitro-4-(trifluoromethyl)benzene **117** and alkylamines **118**.[74] The synthesis proceeded through

the *N*-alkyl-*o*-phenylenediamines **119** formation and finalized with the cyclocondensation reaction between **119** and orthoesters **120**, giving trifluoromethyl substituted products **121** that could be favored their bioactivities compared to their nonfluorinated analogs (Scheme 23a). Two years later, this same group carried out the synthesis and antifungal evaluation of *N*-phenacylbenzimidazoles **123** and their reduction products **124** (Scheme 23b). Compounds **123** and **124** were synthesized in high overall yields (90-95%) *via* *N*-alkylation of 1*H*-benzimidazole **122** with phenacyl bromides **101** and reduction reactions using $NaBH_4$ in methanol, respectively. In general, this study was developed following a similar approach to the one described in the previous section (see Scheme 19b above),[59,63,64] In this case, the synthetic results for benzimidazoles **123** and **124** are better, but the found antifungal activity is lower than in imidazoles **103**-**105**.

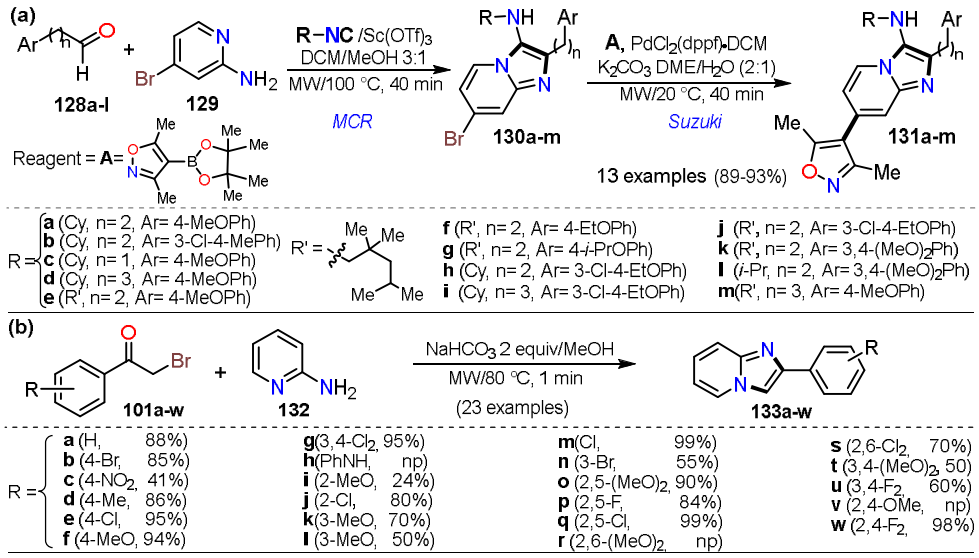
Regarding the synthesis of aza-fused 5:6 imidazoles synthesis, Orrego-Hernández, Castillo, and Portilla carried out the MW-assisted synthesis of 7-phenyl-7*H*-purine or 1-phenylimidazo[4,5-*d*]pyrimidine **127** *via* a pseudo-tetra-component reaction between a molecule of 2-(phenylamino)acetonitrile **125** and three molecules of formamidine acetate **126**, which proceeds in yield moderate (Scheme 23c).[77] For this reaction, 6.0 equiv of the amidine **125** were introduced in two portions to maximize the formation of 4-aminoimidazole intermediate **127'**. In addition, the substrate **126** was prepared by a Cs_2CO_3-promoted direct and highly chemoselective *N*-alkylation of aniline with bromoacetonitrile, two easily accessible reagents allowing access in only two steps to complex molecules such as the purine **127** (Scheme 23c).[77]



Scheme 23. MW-assisted synthesis of benzimidazoles a) **121** and b) **123**, and of c) 7-phenyl-7*H*-purine.

The Department of Chemistry of the University of Massachusetts recently reported the development of a synthetic route in two-step for the obtention of dimethylisoxazole-attached imidazo[1,2-*a*]pyridines **131** as potent and selective CBP/P300 inhibitors.[78] This synthetic methodology consisted of MCR between aldehydes **128**, 2-amino-4-bromopyridine **129**, and isonitrilos, followed by a Suzuki cross-coupling reaction on the heteroaryl bromide **130**, where products **131** were obtained in yields up to 95% (Scheme 24a). Analogously, de la Cruz and co-workers developed the synthesis of imidazo[1,2-*a*]pyridines **133** by utilizing the reaction of phenacyl halide derivatives **101** and 2-aminopyridine **132** as strategic intermediates (Scheme

24b).[79] These series of reactions were performed under environmentally benign conditions and conceded the obtention of compounds with various uses such as biomarkers, photochemical sensors, and drug-like leads.



Scheme 24. MW-assisted synthesis of substituted imidazo[1,2-a]pyridines a) **131** and b) **133**.

5. Systems bearing triazole rings

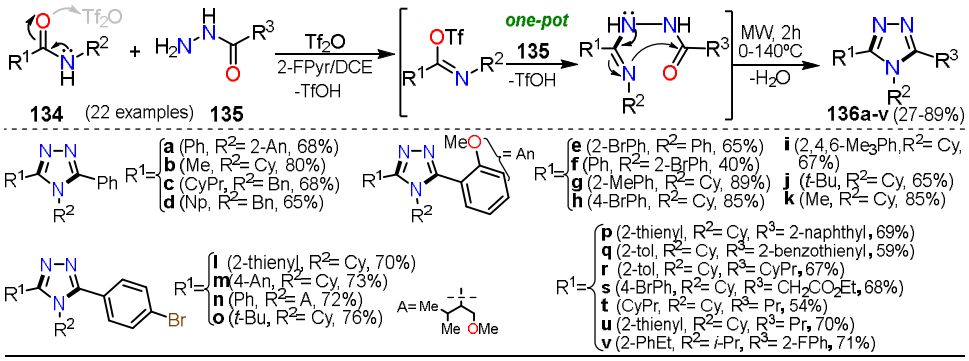
This family of compounds has attracted significant interest in the past decades, principally in medicinal and coordination chemistry fields, as well as in materials science.[1,14,80-84] For example, the 1,2,4-triazole scaffold is frequently found in a wide range of biologically active pharmaceuticals like fluconazole, maraviroc, triazolam, and sitagliptin; an antifungal, antiviral, a sedative, and a drug used to treat diabetes, respectively. The biological effect of 1,2,4-triazole is exceptional.[10,80,81]

The 1,2,4-triazole derivatives can also be employed as an amide cis-bond isostere for peptide mimicry and drug design, improving the pharmacological properties of lead compounds. In addition, they exhibit some photophysical properties that make them objects of interest in the search for ligands in mononuclear and oligo-nuclear medicinal chemistry. Namely, it was proved that incorporating a 1,2,4-triazole ligand into heteroleptic iridium(III) complexes produced sky-blue emissions for potential applications in OLEDs.[80] Due to the applications this triazole core presents, several synthetic approaches for its obtention have been carefully studied. The most common include the Pellizzari synthesis, the Einhorn-Brunner synthesis, syntheses starting from amidines, acyl-hydrazide, hydrazines, amidrazone, and thiosemicarbazone.[1]

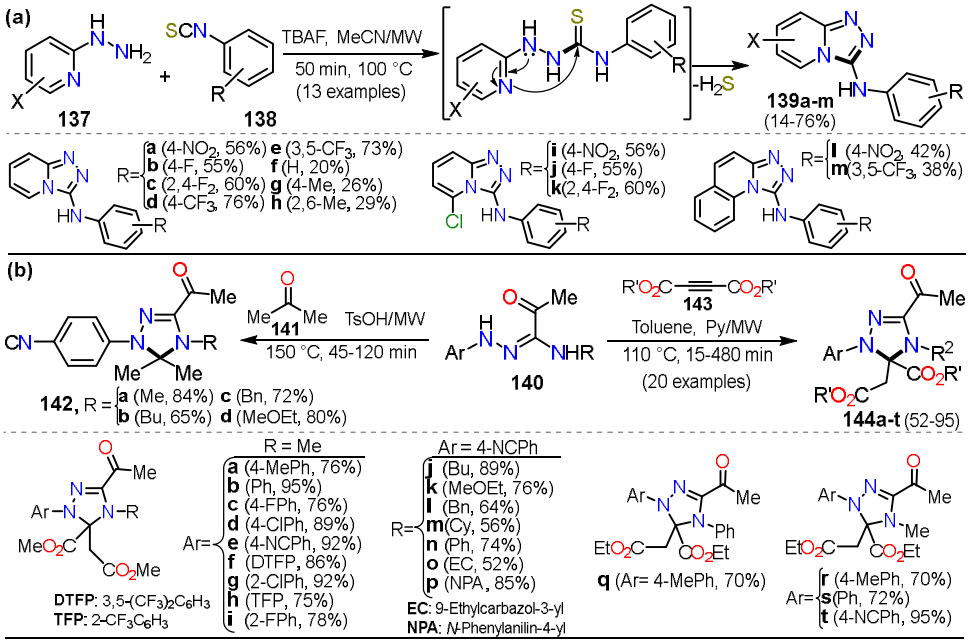
In the same line, 1,2,3-triazoles exhibit crucial bioactive properties; thus, the heterocyclic core is found in several drug-like compounds, which enclose antiviral, antibacterial, antifungal, anti-inflammatory, and anticancer activity. These characteristics are due to some valuable features of triazole scaffolds, such as strong dipole moments, hydrogen bond formation, solubility, dipole-dipole, and π stacking interactions.[1,83,84] The primary synthetic approaches to afford the 1,2,3-triazole moiety include cycloaddition of azide to activated alkenes, azide to allenes, and azide to ketene acetals, and ring transformations.[1,83,84] Further on, MW-assisted synthesis for the obtention of 1,2,4- and 1,2,3-triazoles will be presented. The first example presented regarding the MW-assisted synthesis of triazole derivatives involves the work reported by Charette and co-workers. They developed a method for the one-pot MW-assisted synthesis of 3,4,5-trisubstituted 1,2,4-triazoles **136** (Scheme 25).[80]

The formation of 1,2,4-triazoles **136a-v** took place by the cyclocondensation reaction between secondary amides **134** and aryl- or alkylhydrazides **135**, and using triflic anhydride (Tf_2O) initiation followed by MW irradiation using a one-pot strategy. The triazole ring in **136** is shown to be a functional

directing group for Ru-catalyzed C-H arylation (Scheme 25).[80] In the same line, Scanlan and its research group, developed another method thoroughly described to obtain 1,2,4-triazoles by a one-pot synthesis of [1,2,4]triazolo[4,3-*a*]pyridin-3-amines **139** starting from 2-pyridylhydrazines **137** and thiosemicarbazides **138** (Scheme 26a).[81] Recently, Belskaya *et al.* developed the synthesis of 4,5-dihydro-1*H*-1,2,4-triazoles **142** and **144** using MW-assisted reactions of amidrazones **140** with acetone **141** or acetylenedicarboxylic acid esters **143**, respectively, in the presence of pyridine and toluene as solvent (Scheme 26b).[85]



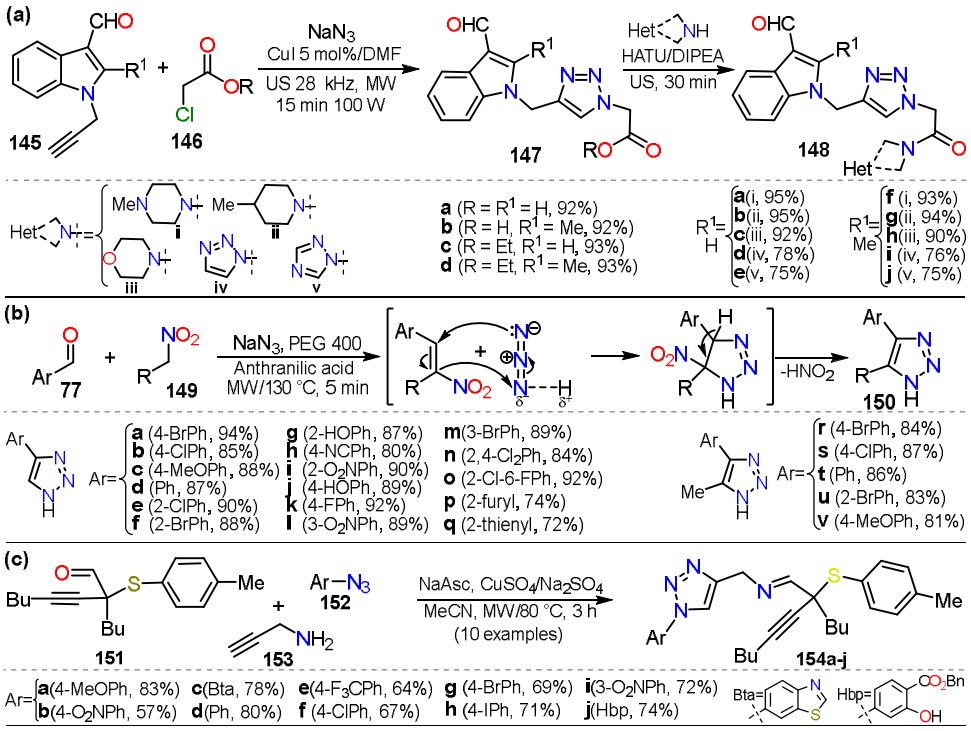
Scheme 25. One-pot MW-assisted synthesis of 1,2,4-triazoles **136a-v**.



Scheme 26. MW-assisted synthesis of a) fused triazoles **139** and b) 1,2,4-triazoles **142** and **144**.

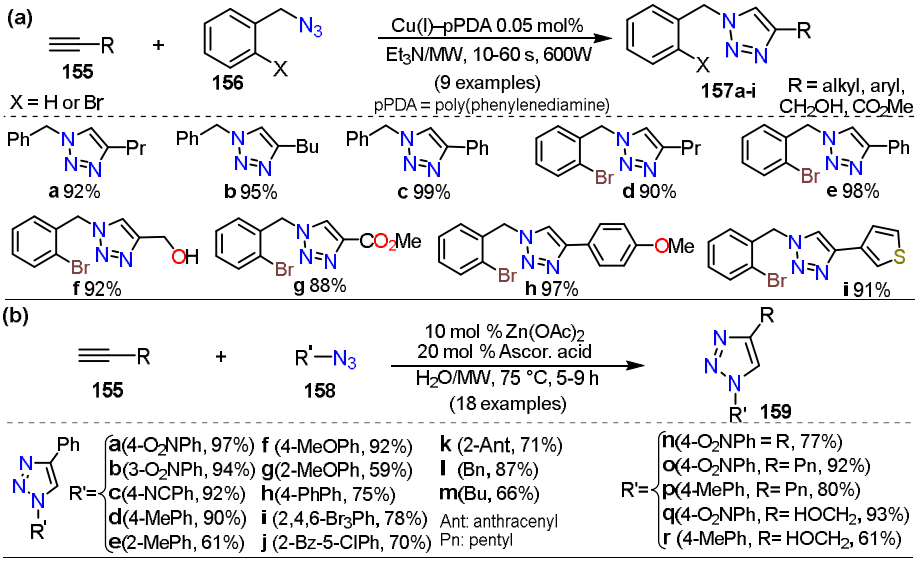
On the other hand, the 1,2,3-triazole derivatives **147** syntheses, an environment-friendly, high yielding, one-pot protocol for the click reaction between *N*-propargyl-3-formylindole **145**, chloroacetic acid/ester **146**, and sodium azide was recently developed by Mokariya and co-workers (Scheme 27a).[86] Compounds **147** were subjected to amidation reaction with secondary amines to afford the amides triazole derivatives **148**. Notably, the obtained triazoles **147** and **148** were tested for their *in vitro* antimicrobial activity against a

panel of pathogenic strains, and several of them shown inhibitory action against *E. Coli*, *S. Typhi*, *P. Aeruginosa*, *C. tetani*, *S. aureus*, and *B. subtillis*. In a similar approach, a MCR of arylaldehydes **77**, nitroalkanes **149**, and sodium azide using anthranilic acid as an organocatalyst under MW irradiation was performed to synthesize the *N*-unsubstituted-1,2,3-triazole derivative **150**. By using this protocol, gram-scale synthesis of biologically important molecules was successfully carried out (Scheme 27b).[87] Another way of synthesizing substituted 1,2,3-triazoles **154** consisted in a MW-assisted MCR involving α-thio-aldehydes **151**, arylazides **153**, and propargylamine **152** (Scheme 27c). This reaction is characterized by forming an imine that *in situ* reacts with **153** by Cu-catalyzed [3+2] azides-alkyne cycloaddition (CuAAC). The reaction results in a family of imines based on 1,4-disubstituted 1,2,3-triazoles.[88]



Scheme 27. Synthesis under MW of 1,2,3-triazole derivatives a) **147** and **148**, b) **150**, and c) **154**.

A similar approach allowed the one-step synthesis of 1,2,3-triazoles **157** *via* a MW-assisted azide-alkyne cycloaddition reaction using a polymer-supported copper(I) composite as a catalytic species in the 1,3-dipolar cycloaddition reaction between terminal alkynes **155** and benzyl azides **156** (Scheme 28a). The catalyst, synthesized using a one-step chemical synthesis route under ambient conditions, was also effective for the MC synthesis of 1,2,3-triazoles from organic halides, sodium azide, and terminal alkynes.[89] As the last example presented in this chapter, Postnikov *et al.* reported a regioselective synthesis of azide-alkyne cycloaddition (AAC) in the presence of $Zn(OAc)_2$ to obtain 1,4-disubstituted triazoles **159** by the reaction of terminal alkynes **155** with arylazides **158**. The authors emphasize that the catalytic system is inexpensive and environmentally friendly in neat water and, in addition, that this is extremely sensitive to steric hindrance in the starting acetylenes.[90] As a general conclusion about the 1,2,3-triazoles synthesis through click chemistry, all involved reactions are efficient and proceed in high yields (Scheme 28b).[14,86-90]



Scheme 28. MW-assisted synthesis of 1,2,3-triazoles a) **157** and b) **159** using simple terminal alkynes.

4. Conclusion

From literature related to the current approach based on MAOS of five-membered *N*-heteroaromatic compounds, it is evident that works from 2015 to 2021 are very important. Thus, it is impossible to present everything in this chapter. However, we developed a strategic approach with an analysis of representative examples to deliver a current contribution to the interested research community in the organic synthesis field. Valuable works have been select concerns MAOS of pyrroles, pyrazoles, imidazoles, triazoles, and their aza-fused 5:6 derivatives. Pyrrole ring classical access includes cyclocondensation and cycloaddition reactions. The most common approach to afford pyrazole derivatives is based on reactions between hydrazine derivatives with 1,3-bis-electrophilic compounds. There is interest in developing synthetic methods based on catalysis, MCRs, and the classic Debus and Bredereck synthesis for imidazole derivatives. Aza-fused 5:6 triazoles are scarce, but syntheses of 1,2,4-free-triazoles were thoroughly described by know synthetic methods like Pellizzari and Einhorn-Brunner synthesis; likewise, the primary synthetic methods to afford the 1,2,3-triazole ring include the Cu-catalyzed [3+2] azides-alkyne cycloaddition (CuAAC).

On the other hand, all five-membered *N*-heteroaromatic compounds herein presented exhibited a wide range of biological activities and photophysical properties due to their heteroaromatic character. As a result, these compounds offer great applications in pharmaceuticals, medicinal chemistry, industrial fields, materials science, and molecular and ions recognition towards molecular probes design. Implementing these scaffolds in the obtention of biologically active compounds allows foreseeing a promising future in chemical synthesis and biochemical and physiochemical research. Additionally, despite numerous published works in this field, several have been developed without a rational approach to the technology presented herein. Thus, a good look at this chapter could improve this issue for diverse investigations.

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