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Review

Recent Advances in Synthesis and Properties of Pyrazoles

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Abstract: Pyrazole-containing compounds represent one of the most influential families of *N*-heterocycles due to their proven applicability and versatility as synthetic intermediates in preparing relevant chemicals in biological, physical-chemical, material science, and industrial fields. Therefore, synthesizing structurally diverse pyrazole derivatives is highly desirable, and various researchers continue to focus on preparing this functional scaffold and finding new and improved applications; this review highlights some of the most recent and strategic examples regarding the synthesis and properties of different pyrazole derivatives, mainly reported from 2017–present. The discussion involves strategically functionalized rings (i.e., amines, carbaldehydes, halides, etc.) and their use in forming various fused systems, predominantly bicyclic cores with 5:6 fusion taking advantage of our experience in this field and the more recent investigations of our research group.

Keywords: acylpyrazoles; aminopyrazoles; bioactivities; photophysical; synthetical utility

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1. Introduction

Pyrazole derivatives are a special class of *N*-heterocyclic compounds (NHCps) bearing a heteroaromatic five-membered ring with two adjacent nitrogen atoms in the annular structure, one pyrrole-type (proton donor) and one pyridine-type (proton acceptor). Pyrazoles can act as weak bases or acids, with possible strength highly dependent on the nature of their substituent groups. The other three positions in the ring permit structural variants starting from the appropriate precursors or using post-functionalization reactions once the pyrazole ring is formed [1–5]; these variations give the pyrazoles diverse and valuable synthetical, biological, and photophysical properties; indeed, more complex structures with various relevant examples can be formed from them (Figure 1) [1–9].

Some fused pyrazoles also have demonstrated different biological activities, exceptional photophysical properties, and high synthetical versatility that allow the obtention of industrially and pharmaceutically crucial chemicals [1–9]; thus, synthesizing pyrazole derivatives efficiently and selectively is an important area of organic chemistry. For instance, pyrazoles have biological activities in many specific areas, such as anticancer, antibacterial, antifungal, antioxidant, and anti-inflammatory, among others [1,8]. Many drugs containing pyrazole core have been reported, such as the analgesic antipyrine, the arthritis treatment phenylbutazone, the non-steroidal anti-inflammatory drugs (NSAIDs): Lonazolac, Rimonabant, and ramifenazone, etc. (Figure 2a) [10,11]; moreover, drugs involving axitinib, zaleplon, reversan, sildenafil, and tracazolate, are exciting fused systems (Figure 2b) [6,12–15]. On the other hand, some pyrazoles, pyrazolo[1,5-*a*]pyrimidines, and pyrazolo[3,4-*b*]pyridines have exhibited excellent physicochemical properties [7,16].

Inside the last-mentioned features, the photophysical properties have been extensively studied because they allow research in environmental, biological, and industrial fields; these features in *N*-heteroaromatic pyrazole derivatives are unique given that saturated NHCps behave analogously to open-chain compounds. Thus, pyrazole derivatives with conjugation properties tend to be molecules with unique and intrinsic photophysical

properties, which can be employed to develop sensors and organic materials [17–21]. One of the most studied topics is the detection of ions [7,20,21] (Figure 3).

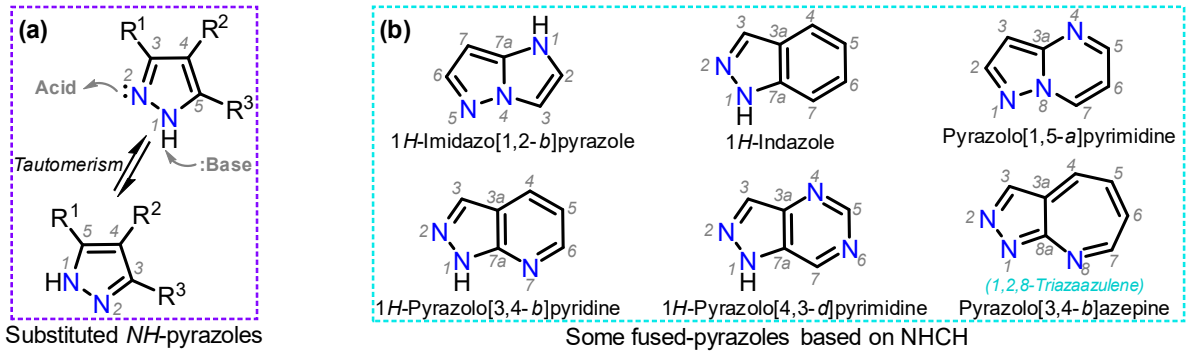


Figure 1. Structure of (**a**) *NH*-pyrazoles and (**b**) some fused pyrazoles with peripheral numbering.

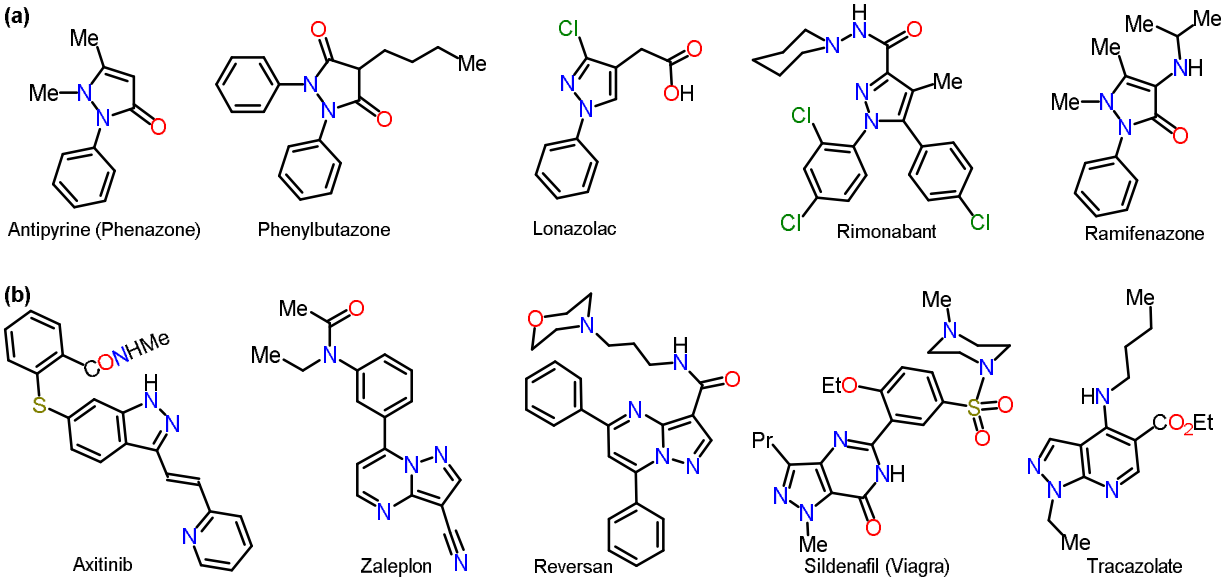


Figure 2. Structure of different drugs based on (**a**) pyrazoles and (**b**) some of their 5:6 fused systems.

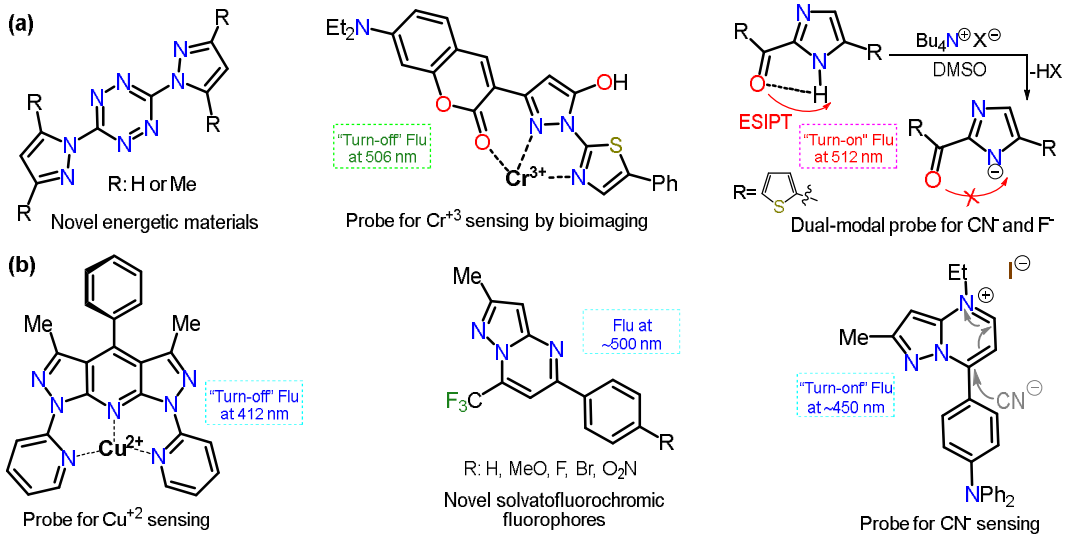
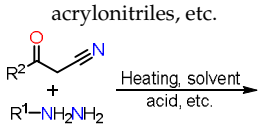
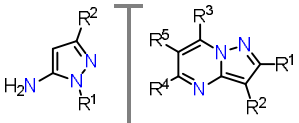
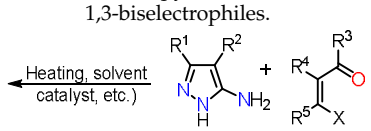
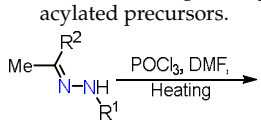
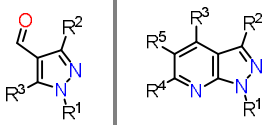
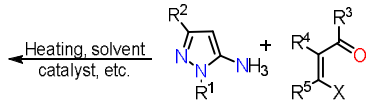
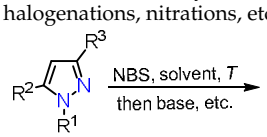
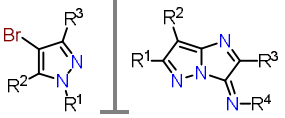
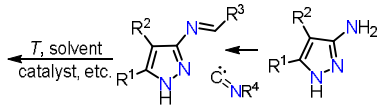


Figure 3. Physically relevant molecules based on (**a**) pyrazoles and (**b**) their fused systems.

Many ions play an essential role in biological and environmental processes; however, in excess, they may result in toxicity, making it an important topic to discover more accessible and manageable ways to detect and quantify them. Anions are more challenging due to their increasing diffuse charge compared with the corresponding isoelectronic cations, a large variety of geometries, and greater pH dependence [7]; they are heavily solvated by polar solvents, making them more challenging to detect on aqueous samples [20]. Molecular sensors have been used for this purpose since they help overcome several problems of conventional methods such as expensive equipment and complex and time-consuming process [21]; they also provide high sensitivity, specificity, and selectivity.

The chemistry of pyrazole derivatives has been extensively documented for several years due to their synthetic versatility and applicability in diverse fields [1–7,22,23]. Despite rings with oxygen or sulfur atoms being part of some fused pyrazole derivatives, nitrogenous rings predominate in heteroaromatic structures (Figure 1b). Thus, this contribution focuses on the recent advances in synthesizing pyrazoles and some of their aza-fused derivatives, mainly in the last five years; moreover, an approach to the biological or photophysical properties of some compounds is described. In general, this review was conceptualized considering our expertise in pyrazole derivatives chemistry, and we hope that it will be a helpful contribution to further applications in the area. A schematic summary depicting the most pertinent syntheses discussed in this work is shown in Table 1.

Table 1. Overview of synthesis of pyrazole derivatives [a].

Synthesis and Functionalization		Pyrazole Derivatives	Synthesis of Fused Pyrazoles	
Section 2.1	Aminopyrazoles: β-ketonitriles, β-enaminonitriles, acrylonitriles, etc. 		Pyrazolo[1,5-*a*]pyrimidines: NH-aminopyrazoles and 1,3-biselectrophiles. 	Section 3.1
Section 2.2	Acylpyrazoles: Vilsmeier-Haack conditions and using already acylated precursors. 		Pyrazolo[3,4-*b*]pyridines: NR-aminopyrazoles and 1,3-biselectrophiles. 	Section 3.2
Section 2.3	Further functional Pyrazoles: halogenations, nitrations, etc. 		Other fused rings: imidazopyrazoles, pyrazoloazepines, indazoles, etc. 	Section 3.3

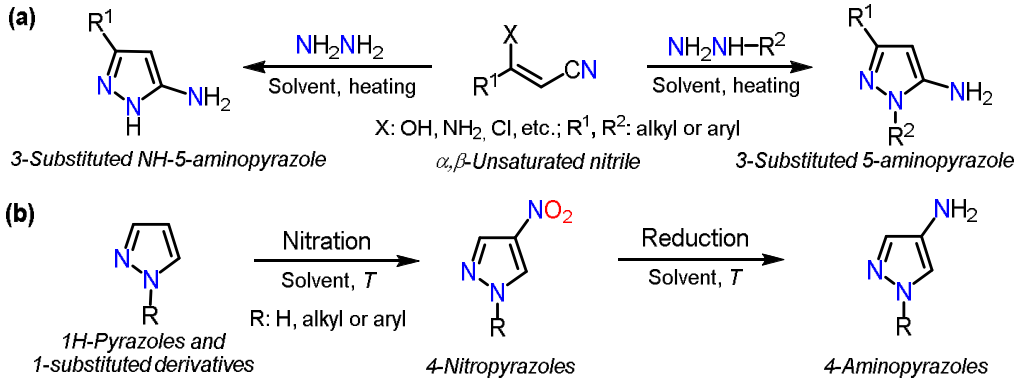
[a] General examples of some relevant synthetical ways involving pyrazole derivatives are shown.

2. Synthesis and Functionalization of Pyrazoles

Due to the relevance of pyrazole derivatives applications, it is crucial to understand their different synthetical approaches to continue innovating around the pyrazole ring; this scaffold construction is carried out via classical cyclocondensation reactions of 1,3-biselectrophilic compounds with hydrazine derivatives or by [3 + 2] cycloaddition reactions of diazo compounds with different alkynes [4,10]. Pyrazoles classical synthesis requires harsh reaction conditions, high temperatures, organic solvents that often are toxic and volatile, and extensive reaction times; this long time has significant energy waste, increasing the final synthesis cost. Thus, protocols continue to be improved to maximize synthetical efficiency, cost, time, eco-compatibility, and the economic aspect. For example, multicomponent reactions (MCR) are reported to generate the intermediate reagents in situ; in addition,

both ultrasound (US) and microwave (MW) assisted organic synthesis are tools to reduce the solvent quantity and reaction purification [19,24].

As previously mentioned, pyrazoles can be functionalized by introducing diverse groups in the starting reagents or by aromatic substitution reactions on the pyrazole ring [4,24]. For example, α,β-unsaturated nitriles bearing an easily displaceable group at Cβ react with hydrazine derivatives to generate 5-aminopyrazoles; as observed, the amino group is obtained directly from the starting material (Scheme 1a). On the other hand, Scheme 1b shows the synthesis of 4-aminopyrazoles using a post-functionalization strategy involving the reduction reaction of a nitro group previously introduced via an electrophilic aromatic substitution (AES) reaction on an unsubstituted ring; this contribution shows examples of similar approaches in Scheme 1: functionalizations through the ring construction or aromatic substitution reactions.



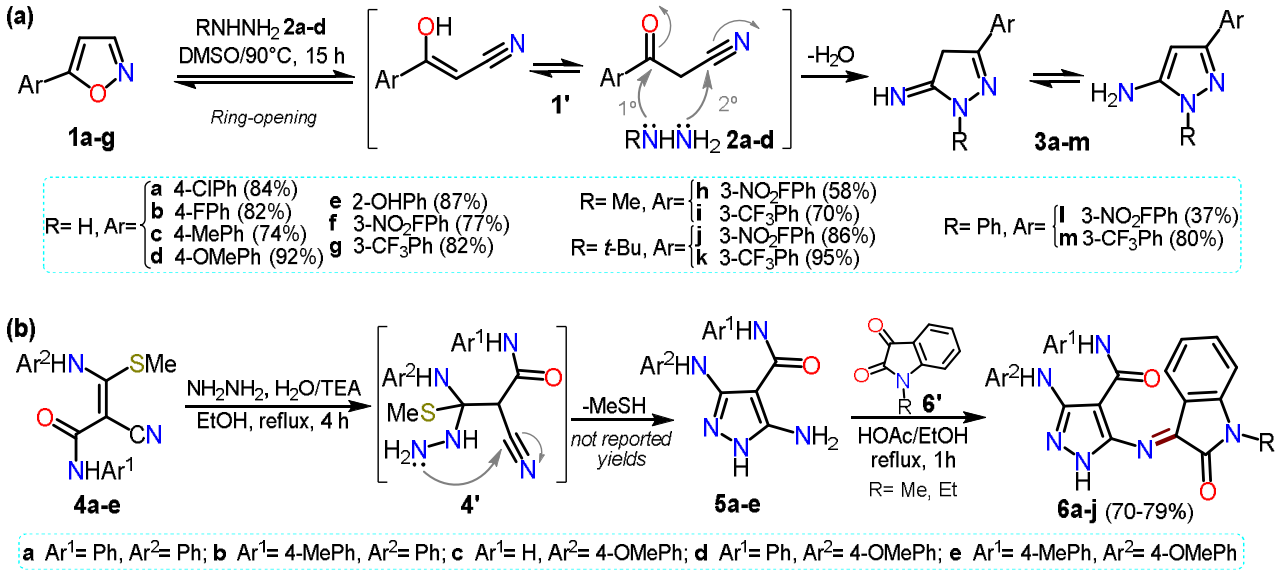
Scheme 1. Synthetical methodologies for (**a**) 5-aminopyrazoles and (**b**) 4-aminopyrazoles.

In the following sections of this chapter, we will discuss various synthetical protocols, mainly reported from 2017–present, to access important functionalized pyrazoles such as aminopyrazoles, acylpyrazoles, halopyrazoles, and other interesting systems.

2.1. Aminopyrazoles

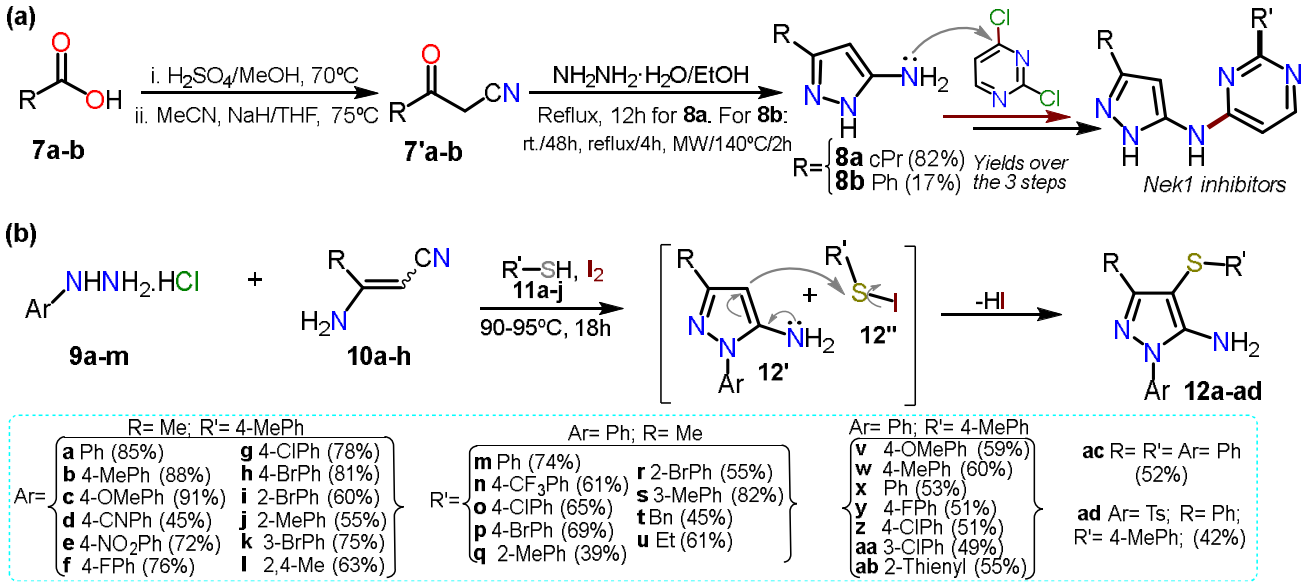
We start this chapter by discussing synthetical procedures used to obtain 5-aminopyrazoles, whose chemistry has been well documented for a long time [4,22]. We wanted to expose examples from the last five years; however, other earlier key examples are worth mentioning. For instance, we have decided to mention the work reported in 2016 by Kallman et al. [25], which is not a standard procedure for accessing 5-aminopyrazoles. Specifically, the authors reported a regioselective synthesis of aminopyrazoles from isoxazoles **1a–g** as they are synthetic equivalents of ketonitriles **1′**. The reaction proceeds via ring-opening, generating a ketonitrile **1′** intermediate that then reacts with hydrazine derivatives **2a–d** to form the respective cyclocondensation product **3a–m** (Scheme 2a).

In 2021, Hassan and co-workers [26] reported the synthesis of pyrazole-oxindole hybrid systems **6a–g** by the condensation reaction of 5-aminopyrazoles **5a–e** with *N*-substituted isatin **6′** (Scheme 2b). Heteroamines **5a–e** were obtained by the cyclocondensation reaction of *N*-aryl-3-(arylamino)-2-cyano-3-(methylthio)acrylamides **4a–e** with hydrazine hydrate (**2a**). Intermediates **5** are substituted with arylamines and amides at positions 3 and 4, making it possible for the core to have a wide range of post-functionalizations. In this case, final products **6a–j** were used for in vitro cytotoxicity assays against four human cancer-type cells; it is important to note that in the examples about 5-aminopyrazoles synthesis mentioned above, and in most others involving ketonitriles or enaminonitriles as 1,3-bis-electrophilic substrates, it is necessary to have an easy displacement group on the Cβ of the substrate to generate the required unsaturation in the product.



Scheme 2. Synthesis of 5-aminopyrazoles by (**a**) isoxazole ring-opening and (**b**) from enaminonitriles.

On the other hand, Pilakowski et al. [27] synthesized 5-alkyl-3-amino-1*H*-pyrazoles **8a–b** starting from carboxylic acids **7a–b** (Scheme 3a). First, an esterification reaction was developed, and the respective ester was treated with sodium hydride and acetonitrile to form the corresponding ketonitrile **7′**. Next, this intermediate was treated with hydrazine hydrate to obtain the desired products **8a–b**, which were then coupled to dichloropyrimidine to yield N-substituted pyrazoles tested as Nek1-inhibitors. The low yield of **8b** (17%) versus **8a** (82%) is due to the last step, where the authors subjected the reaction with substrate **7′b** to different conditions; they possibly wanted to obtain the product as the expected light yellow solid; however, they only managed to isolate it as a viscous orange oil.

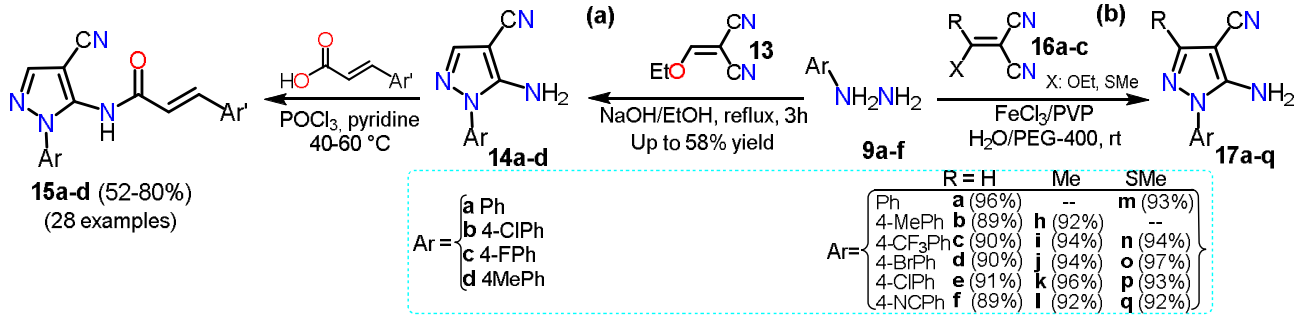


Scheme 3. 5-Aminopyrazole synthesis forms (**a**) carboxylic acids and (**b**) enaminonitriles.

In another recent approach, Annes et al. [28] reported a free-metal and free-solvent multicomponent synthesis mediated by iodine to obtain aminopyrazole-thioether derivatives **12a–ad** in the range of 39–91% yield. The multicomponent reaction comprises substituted hydrazines **9a–m**, nitriles **10a–h** benzenethiols **11a–j**. Reagents **9a–m** and **10a–h** undergo a Michael reaction in the presence of Lewis acid, followed by intramolecular cyclization with

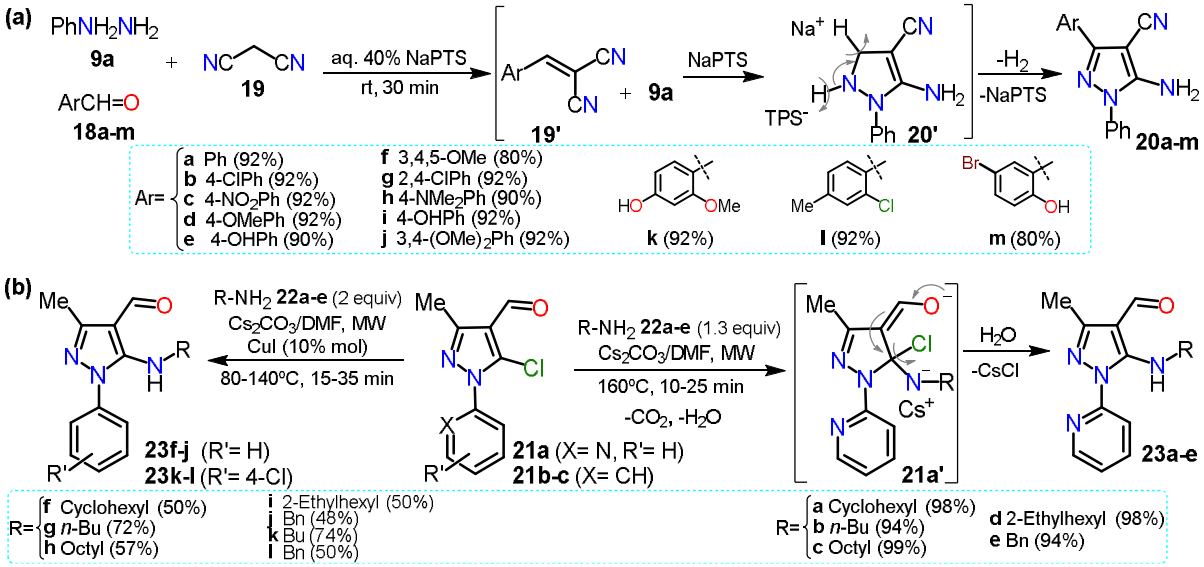
the elimination of ammonia to afford 5-aminopyrazoles **12′**. At the same time, iodine reacts with **11** to form the electrophilic derivative **12″**. Finally, the C-S bond was formed via an electrophilic aromatic substitution (EAS) reaction on **12′**. The reaction scope was studied, including diverse aromatic and aryl groups at positions 1, 3, and 4 (Scheme 3b); this reaction proceeded with a wide range of substrates; however, the best yields are obtained when the aminopyrazole **12′** has an electron releasing group (ERG) or the electrophilic reagent **12″** has an electron-withdrawing group (EWG).

In 2018, Ren et al. [29] synthesized 5-amino-1-arylpyrazole-4-carbonitriles **14a–d** starting from a mixture of arylhydrazine hydrochloride **9a**, 2-(ethoxymethyl)malononitrile **13**, ethanol, and sodium hydroxide via a classical cyclocondensation reaction (Scheme 4a). With 5-aminopyrazoles **14a–d** in hand, the authors transformed them into the carboxamide derivatives **15a–d**, which then were evaluated against three fungal strains and as inhibitory compounds against succinate dehydrogenase. A year later, Elnagdy and Sarma [30] reported a homogenous catalytic system using $FeCl_3$/PVP and green solvent water/PEG-400 to synthesize 4-amino-1-aryl-1*H*-pyrazole-4-carbonitriles **17a–q** using a cyclocondensation reaction of arylhydrazines **9a–f** with malononitrile derivatives **16a–c**. A mixture of $FeCl_3$ and polyvinyl pyrrolidine (PVP) was used to accelerate the addition of **9a–f** to the double bond of **16a–c**; then, an intramolecular cyclization allows the formation of products **17a–q** in up to 97% yield with reaction times of 2–4 h (Scheme 4b).



Scheme 4. Pyrazole synthesis from malononitrile derivatives (**a**) **13** and (**b**) **16a–c**.

In 2020, Sapkal and Kamble [31] obtained 5-aminopyrazole-4-carbonitriles **20a–m** using a green protocol based on a three-component cyclocondensation of phenylhydrazine **9a**, aldehyde derivatives **18a–m**, and malononitrile (**19**) adding sodium *p*-toluenesulfonate (NaPTS) as a catalyst in aqueous media (Scheme 5a). The authors mentioned that NaPTS was used as a hydrotrope that helps increase the solubility of poorly soluble organic compounds in water. First, water hydrates the hydrotrope head groups, decreasing their electrostatic attraction. Both head groups move apart, displacing water molecules interacting with hydrophobic parts; this action helps the reactant molecules interact, enhancing the reaction on aqueous media. The reaction mechanism starts with the nucleophilic attack of **19** on the electrophilic carbon of arylaldehydes **18a–m** to form arlylidenemalononitrile derivatives **19′**. Then, **9a** proceeds by a nucleophilic attack over the double bond of **19′**, and finally, the addition intermediate undergoes intramolecular cyclization to afford products **20a–m**. Although the authors mention that the presence of NaPTS favors the reaction by increasing the solubility of reactants, we believe it mainly helps in the product aromatization step (**20′** in Scheme 5a) as **19′** do not possess a leaving group. For this synthesis, the substituent electronic effects do not influence the yields and scope of the reaction.



Scheme 5. Synthesis of 5-aminopyrazoles from (**a**) malononitriles and (**b**) 5-chloropyrazoles.

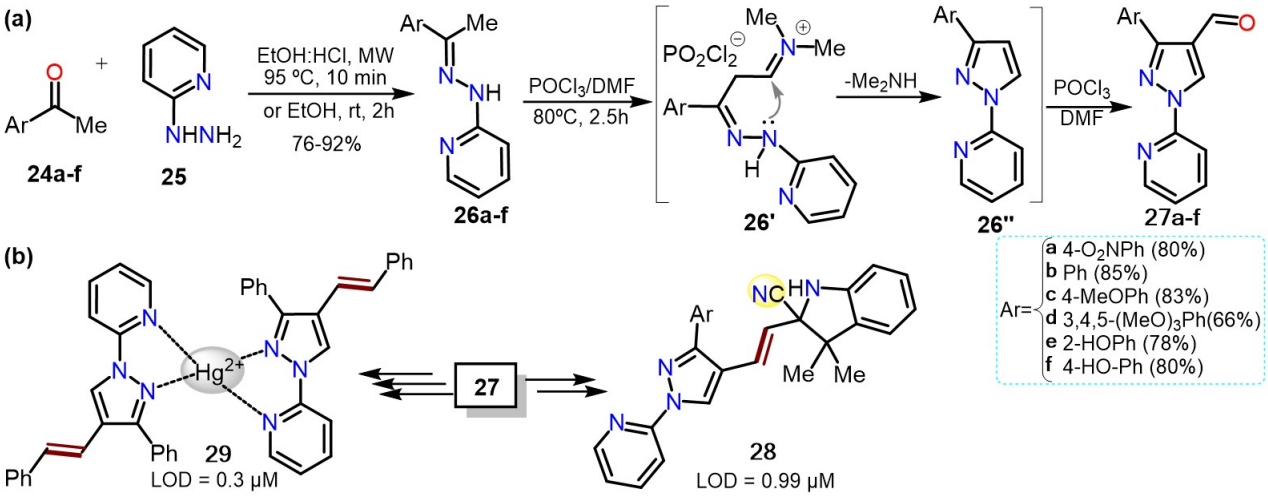
This section started with a "non-classic" method to obtain 5-aminopyrazoles, and in 2015, another not classic strategy was described via a nucleophilic aromatic substitution (NAS) reaction on 5-chloropyrazole derivatives. Specifically, 5-(*N*-alkyl)aminopyrazoles **23a–e** were synthesized in high yields via the microwave-assisted reaction between 5-chloro-4-formylpyrazoles **21a–c** and primary alkylamines **22a–e** [32]. The reaction was possible because the amine nucleophilicity is favored under MW by the cesium effect and the substrate **21a** has a 2-pyridyl group at position 1, which is a strong EWG; however, using the *N*-aryl substituted substrate **21b–c**, the reaction needs harsh conditions and even CuI as a catalyst to form **23f–l**; this reaction type has been scarcely studied since the pyrazole ring exhibits a moderate π-excedent character, which disfavors the initial nucleophilic attack. Therefore, these results corroborate the difficulty of the NAS reaction on pyrazole derivatives justifying its limited study (Scheme 5b).

2.2. Acylpyrazoles

In this section, synthetical methods commonly used to obtain acylpyrazoles are described. Specifically, 4-formylpyrazoles synthesis under Vilsmeier-Haack conditions and the preparation of other acyl derivatives (i.e., ketones, esters, amides, etc.) are discussed.

2.2.1. Formylpyrazoles

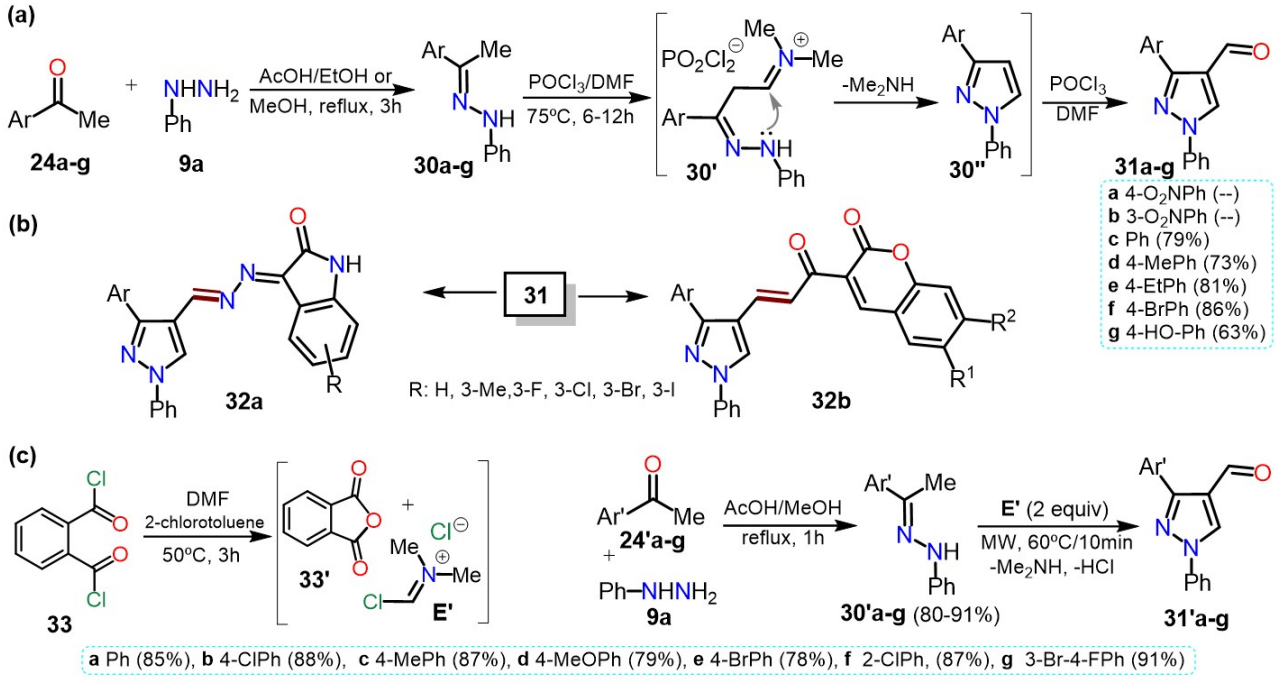
Formylpyrazoles are strategic intermediates in obtaining a wide range of biologically active compounds, with the 4-formyl derivatives being more usual; they possess a high synthetical versatility allowing them a plethora of reactions for the insertion of more functional groups. Our research group has reported the synthesis of 3-aryl-1-(pyridin-2-yl)-1*H*-pyrazole-4-carbaldehydes **27a–f** via Vilsmeier-Haack cyclization-formilation of different hydrazones **26a–f**, which were generated from acetophenones **24a–f** and 2-hydrazinylpyridine (**25**). Precursor **26** was transformed in the 1,3-biselectrophilic intermediate **26′** under Vilsmeier-Haack conditions. Subsequently, **26′** is cyclocondensed to pyrazole **26″**, which is finally formylated to deliver 4-formylpyrazole **27** in 66–85% yields (Scheme 6a).



Scheme 6. Synthesis of (**a**) 4-formyl-1-(2-pyridyl)pyrazoles and (**b**)chemosensors based on pyrazoles.

Notably, heteroaldehydes **27** were successfully used as reagents in chemosensors synthesis to detect cyanide ions (CN^-) [33,34]; for example, indolium salts (hemicyanine derivatives) **28** were synthesized and used as colorimetric probes for CN^- recognition with limits of detection (LODs) of up to 0.99 μM [34]. On the other hand, the 1-(2-pyridyl)-4-styrylpyrazole **29**, obtained from **27** via a Witting olefination followed by a Mizoroki-Heck coupling, was used to detect Hg^{2+} with a LOD of 0.31 μM [35] (Scheme 6b); these LODs values are below the respective limits of the World Health Organization (WHO) [21].

Similarly, Kaur et al. [36] synthesized 4-formyl-1-phenylpyrazoles **31a–f** using the Vilsmeier-Haack reaction with phenylhydrazones **30a–f**, $POCl_3$, and DMF. The corresponding substrates **30a–f** were obtained by a condensation reaction between phenylhydrazine (**9a**) and acetophenones **24a–f** in ethanol using acetic acid as a catalyst (Scheme 7a). In this case, the yields are not particularly dependent on the different substituents.

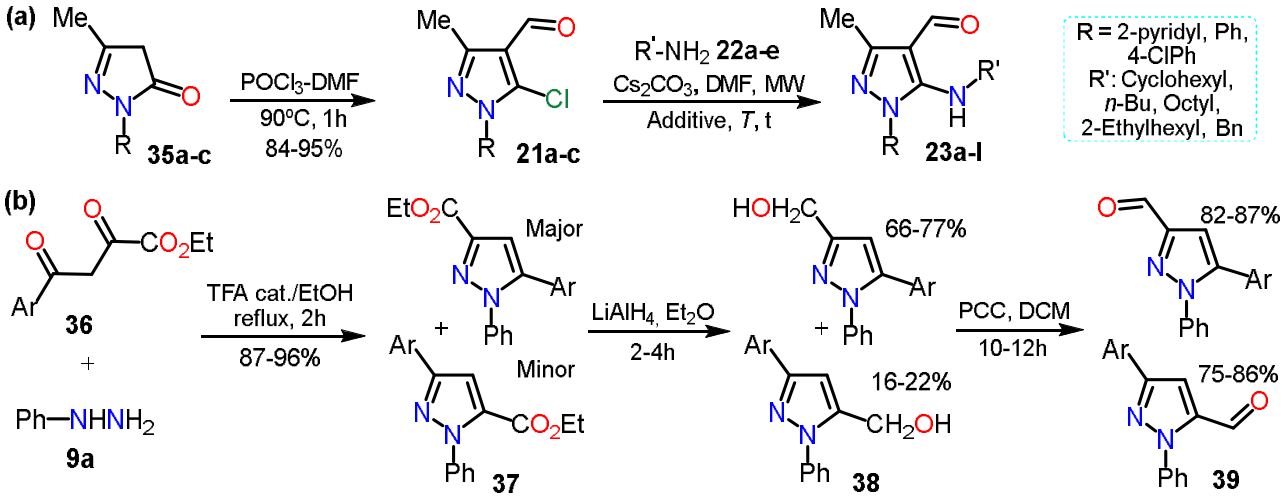


Scheme 7. Synthesis of (**a**) 4-formylpyrazoles and (**b**) biologically activity pyrazoles. (**c**) Reaction de VH using PDC **33**.

From 4-formylpyrazoles **31**, new hybrid isatin derivatives **32a** were obtained and tested for their α-Glucosidase inhibition for controlling postprandial hyperglycemia in diabetic patients. A similar methodology was used by Kumar and co-workers, who synthesized the 4-formylpyrazoles **31c–g** starting from acetophenones **24c–g** and **9a** in yields between 63–86% (Scheme 7b) [37]. The heteroaldehydes **31c–g** were used as intermediates for synthesizing pyrazole-coumarin derivatives **32b**, and their antitubercular activity against the Mycobacterium tuberculosis H37Rv strain was tested.

Most formilations over pyrazole rings are carried out via a classical Vislmeier-Haack (VH) reaction (i.e., $POCl_3$/DMF), and modifications changing the chlorination agent can be performed so as not to use the toxic reagent $POCl_3$. For instance, Kumari et al. [38] synthesized 4-formylpyrazoles **31′a–g** in a similar route that shown in Scheme 7a, that is, through the hydrazone derivative **30′a–g**; nevertheless, the VH reagent was derived from phthaloyl dichloride (PDC, **33**) and DMF (Scheme 7c). Once the electrophile **E′** is formed, the reaction of it with **30′a–g** is performed under MW irradiation to afford products in high yields (78–81%), without particular dependence on the effect of the substituent.

In the previous section, 5-alkylaminopyrazoles **23** were mentioned (see Scheme 5b), where the substrates used for that synthesis were 5-chloro-4-formylpyrazoles **21**, which were obtained from the respective pyrazolones **35**; these starting materials undergo a chloroformylation reaction under Vilsmeier-Haack conditions to afford heteroaldehydes **21** (Scheme 8a). In the next synthetic step, chlorine was substituted, generating only the 5-amino-4-formylpyrazoles **23** chemoselectively [32].

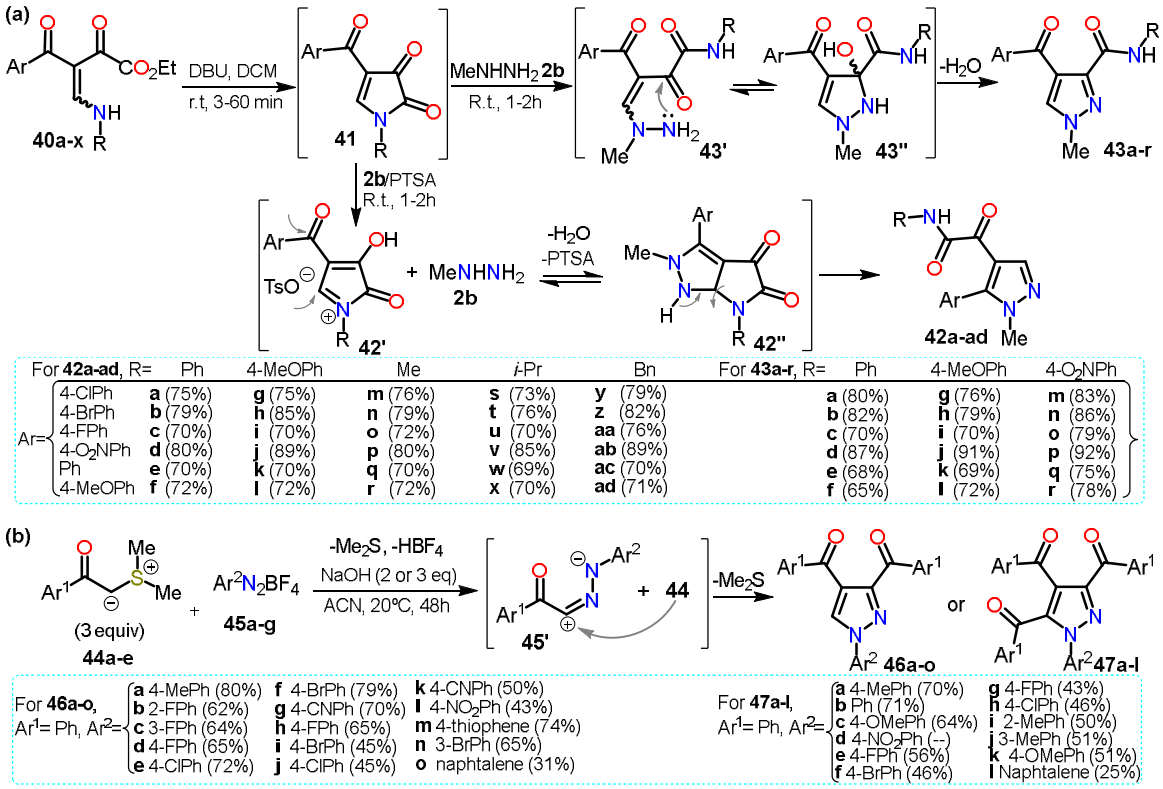


Scheme 8. Synthesis of formylpyrazoles from (**a**) pyrazolones and (**b**) diketoesters.

In practically all the literature about formylpyrazoles synthesis, the Vilsmeier-Haack conditions are used; however, in 2007, Nag et al. obtained 3/5-formyl derivatives **39** in an interesting and unconventional example [39,40] that we decided to consider since we found no more examples of this methodology. For synthesizing products, pyrazole esters **37** were obtained by the cyclocondensation reaction between diketoesters **36a–c** and phenylhydrazine (**9a**). Subsequently, compounds **37** were reduced with $LiAlH_4$ in dry diethyl ether to give the respective pyrazole alcohols **38**, which by PCC-promoted oxidation reaction yielded the desire 3/5-formylpyrazoles **39** in high yields (Scheme 8b).

2.2.2. Other Acylated Derivatives

Regarding other acylpyrazoles, Poletto et al. [41] recently developed a regioselective synthesis of 4,5/3,4-disubstituted *N*-methylpyrazoles **42**/**43** from 4-acyl-1*H*-pyrrole-2,3-diones **41** and methylhydrazine **2b** in the presence or not of acid (Scheme 9a).

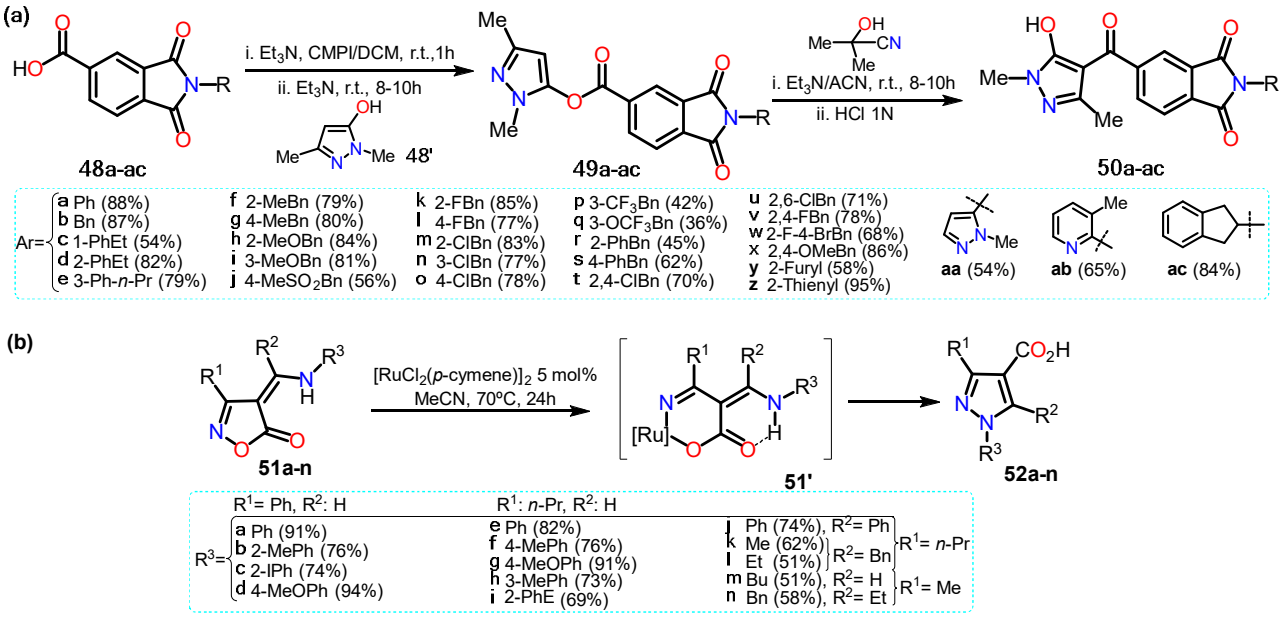


Scheme 9. Synthesis of acylpyrazoles from (**a**) β-enaminodiketones and (**b**) sulfur ylides.

The pyrrole derivative **41** is generated in situ when the β-enaminodiketone **40a–x** is cycled in the presence of DBU. Treatment of the pyrrole-2,3-dione **41** with *p*-toluenesulfonic acid (PTSA) leads to the formation of specie *N*-acyliminium **42′**, which is then converted to the fused system pyrrolo[2,3-*c*]pyrazole **42″**; finally, the cleavage of **42″** affords the 4,5-disubstituted pyrazoles **42a–ad**. The absence of PTSA in the reaction allows **2b** to directly attack C5 of the intermediate **41** followed by cleavage of the pyrrole ring generating a non-cyclic intermediate **43′**. Afterward, an amino group performs a nucleophilic attack on the carbonyl carbon of the α-ketoamide group; ultimately, water elimination in **43″** gives the 3,4-disubstituted pyrazoles **43a–r**. In both cases, high yields were obtained regardless of the substituents used, and various ERGs and EWGs were tested to evaluate the scope of the reaction.

Similarly, Qui et al. [42] reported a divergent domino annulation reaction between sulfur ylides **44a–e** with aryldiazonium tetrafluoroborates **45a–g** to afford tri- and tetra-substituted acylpyrazoles **46a–o** and **47a–l**, respectively; this synthesis proceeded via the interaction of the in situ generated 1,3-dipole **45′** with more molecules of **44** (Scheme 9b).

In a different work, He et al. [43] synthesized acylpyrazoles **50a–ac** from N-substituted isoindoline-1,3-dione derivatives **48a–ac** (Scheme 10a). Precursors **48a–ac** were obtained by reaction between 1,3-dioxo-1,3-dihydroisobenzofuran-5-carboxylic acid with the appropriate primary amine in anhydrous acetic acid. The substrate **48a–ac** and 2-chloro-1-methylpyridinium iodide (CMPI) reacted to then formed the respective pyrazole esters **49a–ac** with 1,3-dimethyl-1*H*-pyrazol-5-ol (**48′**). The esters molecules were then transformed, through a Fries rearrangement, into the final products **50a–ac**; these 4-aroylpyrazoles **50a–ac** were tested for *Arabidopsis thaliana* 4-hydroxyphenylpyruvate dioxygenase (AtHPPD) inhibition activities. For these derivatives, once EWGs were inserted the yields were slowly lower than for those with ERGs.



Scheme 10. Synthesis of acylpyrazoles from (**a**) 1,3-dimethyl-1*H*-pyrazol-5-ol and (**b**) isoxazolones.

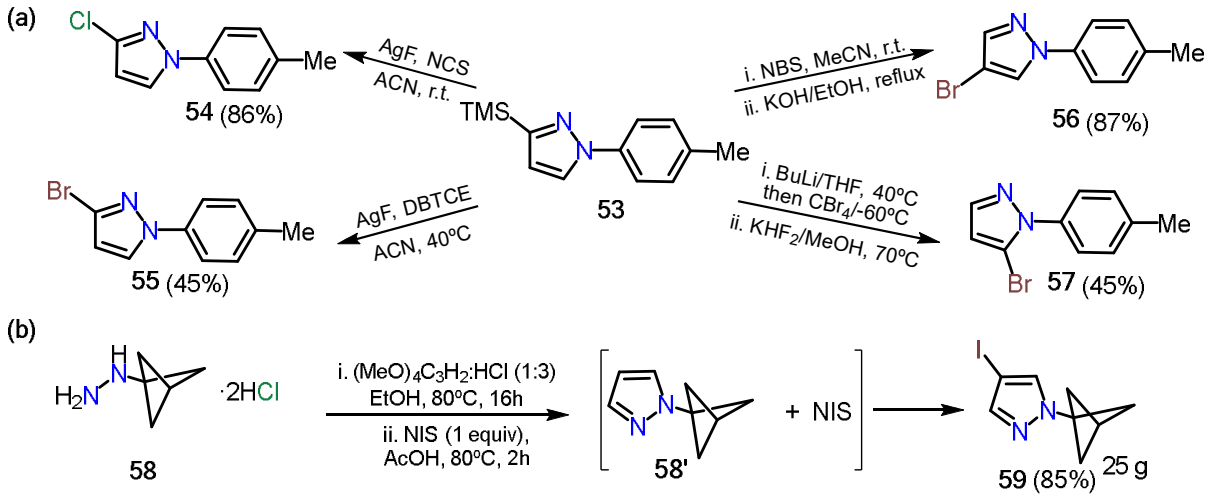
Recently, Loro et al. [44] obtained pyrazole-4-carboxylic acids **52a–n** starting from isoxazole-5(4H)-ones (**51a–n**) using $[RuCl_2(p\text{-cymene})]_2$ as a catalyst. The transformation begins with a ring-opening non-decarboxylative path that generates a vinyl Ru-nitrenoid intermediate that undergoes cyclization to afford the desired pyrazoles (Scheme 10b). Specifically, the catalytic cycle starts with the oxidative addition of catalyst to **51**, generating intermediate **51′**, which is stabilized due to the formation of a hydrogen bonding; this complex undergoes ring-opening resulting in a Ru-nitrenoid intermediate affording the final product via reductive elimination of the metal; it is worth mentioning that the catalytic cycle mechanism is not well elucidated, and the authors explain just a proposal.

2.3. Further Functional Pyrazoles

Considering the broad applicability of pyrazole, in addition to the already discussed examples of the most frequent functionalized pyrazoles (i.e., aminopyrazoles and acylpyrazoles), other functional derivatives bearing substituent groups such as halogens, trifluoromethyl, hydroxyl, pyrenyl, thiophenyl, and nitro, among others are also essentials. Consequently, the below mention will be made of some of these other pyrazoles.

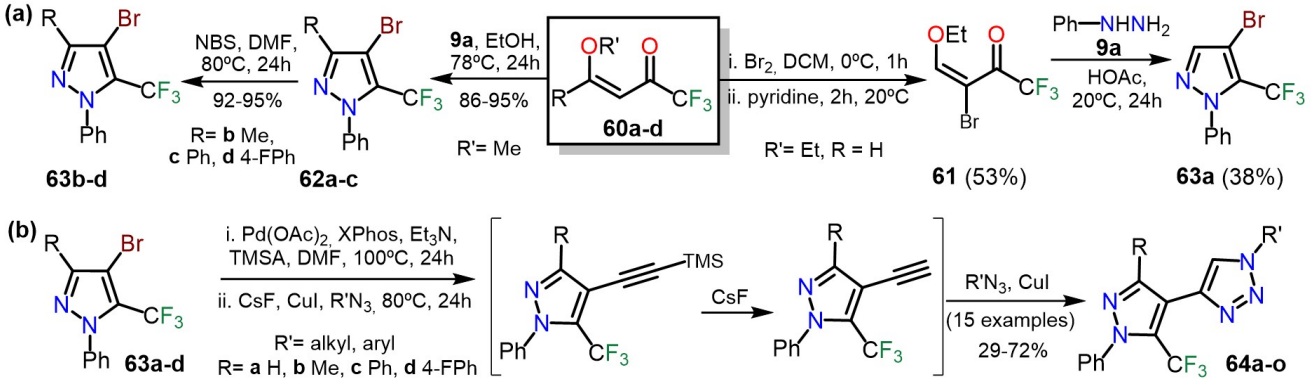
2.3.1. Halopyrazoles

In 2019, Onodera et al. [45] reported a regioselective halogenation of 3-trimethylsilylpyrazole **53** (Scheme 11a). The introduction of halogen atoms at positions 3, 4, and 5 was possible thanks to the different character and orthogonal reactivity of each one; position 3 has the trimethylsilyl group (TMS), which can be easily removed under mild conditions generating a carbanion that can react towards electrophilic substrates such as *N*-chlorosuccinimide (NCS) and 1,2-dibromotetrachloroethane (DBTCE), affording chlorinated **54** and brominated **55** pyrazoles, respectively. On the other hand, position 4 is the most nucleophilic on the ring; therefore, the direct reaction with *N*-bromosuccinimide (NBS) followed by deprotection of the TMS group affords the 1-aryl-4-Bromopyrazole **56**. Finally, position 5 possesses the most acidic proton of the ring; thus, using a base such as *n*-butyllithium and tetrabromomethane, followed by deprotection of TMS, allows a halogenation at position 5 of the pyrazole ring to afford the respective 5-bromopyrazole **57**. A similar approach was recently reported by Zarate and co-workers [46], in which the authors synthesized the 4-iodopyrazole derivative **59** through a condensation/iodination sequence starting from bicyclo[1.1.1]pentan-1-ylhydrazine **58** and using tetramethoxypropane as an additive in the reaction carried out in ethanol (Scheme 11b).



Scheme 11. (**a**) Halogenation of the pyrazole **53** and (**b**) synthesis of the 4-iodopyrazole **59**.

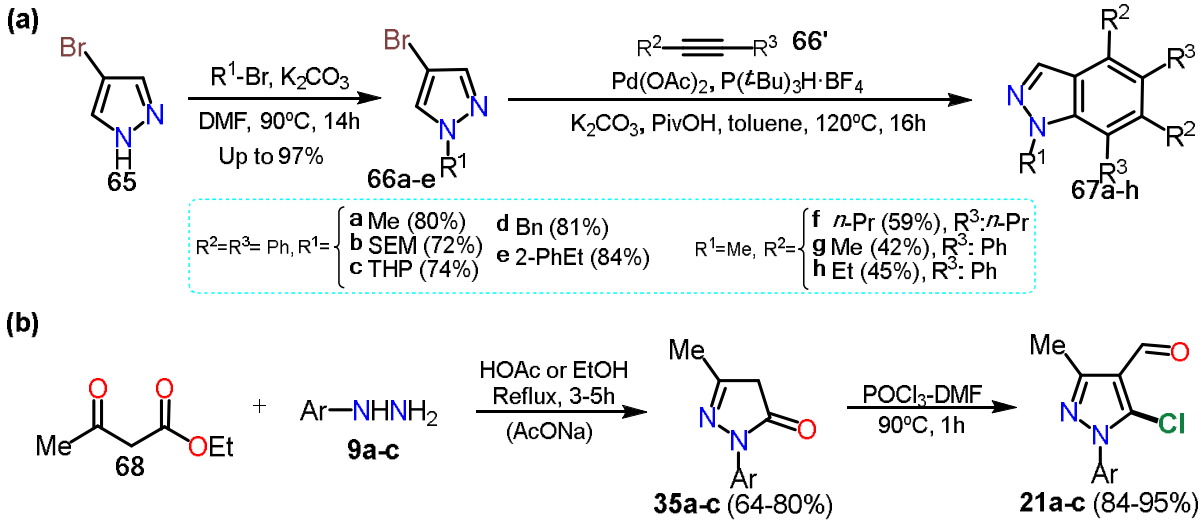
In 2017, Bonacorso et al. [47] Synthesis of 4-bromo-5-(trifluoromethyl)-1-phenyl-1*H*-pyrazoles **63a–d** by two interesting methodologies; the first proceeded through the brominated 1,3-bis-electrophilic substrate **61** whereas, in the second, the pyrazole ring in **62** was brominated using NBS as the brominated agent. The synthesis of **63a–d** was developed by utilizing 1,1,1-trifluoro-4-methoxy-alken-2-ones **60a–d** as starting reagents. On the one hand, substrate **60a** was brominated and then cyclocondensed with phenylhydrazine (**9a**) to form product **63a**. On the other hand, **60b–d** cyclocondensed with **9a** to obtain pyrazoles **62a–c**, which finally brominated to obtain products **63b–d** (Scheme 12a). Compounds **63a–d** were successfully used in the one-pot three-step synthesis of polysubstituted 4-(5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-1*H*-1,2,3-triazoles **64a–o**; they carried out a sequential Sonogashira cross-coupling, desilylation, and a copper(I)-catalyzed azide-alkyne cycloaddition reaction (CuAAC) with high overall yields. The authors cited that the CF_3 group in **63** made the Sonogashira cross-coupling reaction challenging (Scheme 12b).



Scheme 12. Synthesis of (**a**) 4-bromo-5-(trifluoromethyl)pyrazoles and their (**b**) synthetical utility.

As we can see, in the above approaches, halogenation of the pyrazole is carried out once the ring; however, other methods use the commercial halogenated pyrazole as a start reagent in the synthesis of more complex structures; these protocols exist due to the versatility of halosubstituted products, allowing different reactions such as aromatic substitutions on the rings or coupling reactions to form new C–C bonds. For example, Tsui and collaborators [48] used 4-bromopyrazoles **66a–e** in palladium-catalyzed benzannulation to obtain substituted indazoles **67a–h**. The presence of bromine facilitates the oxidative addition step on C4; it is important to note that despite some halopyrazoles being commercial, various halogenated substrates are obtained by other transformations that do not involve direct

halogenation; in this respect, the Tsui group synthesized the *N*-alkyl-4-bromopyrazole derivative **66e** by the respective *N*-alkylation reaction of 4-bromo-1*H*-pyrazole (**65**) and alky bromides potassium carbonate-mediated in DMF (Scheme 13a).



Scheme 13. Synthesis of (**a**) indazoles from 4-bromopyrazoles and of (**b**) 5-chloropyrazoles.

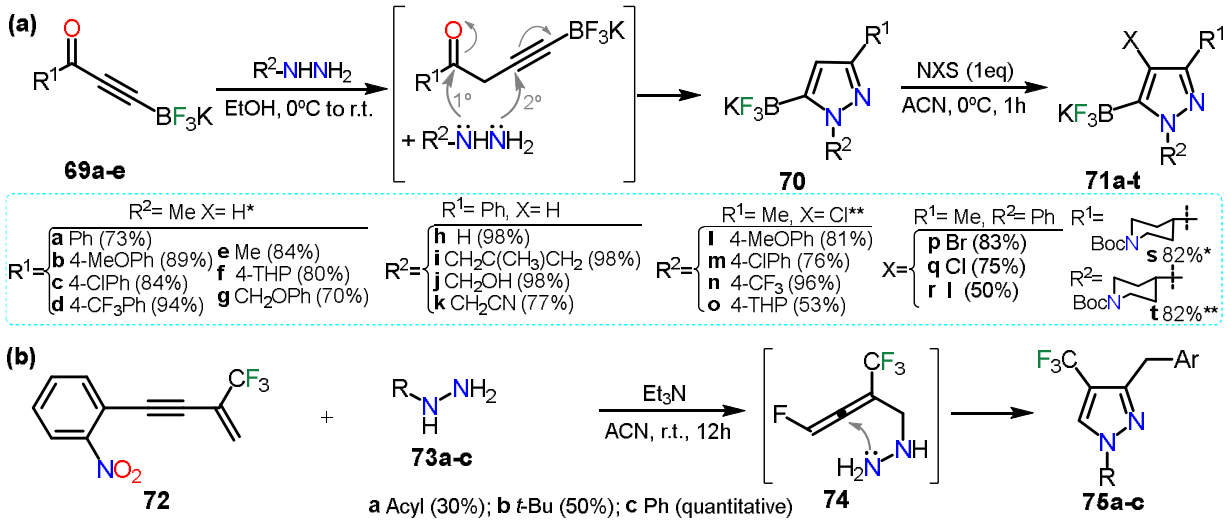
In the above sections, we cited the previous work of Orrego-Hernandez et al. [32], in which 5-alkylaminopyrazoles **23** were obtained through NAS reactions on 5-chloro-4-formylpyrazoles **21** and using primary alkyl amines as nucleophiles. The substrates **21** were obtained by the chloroformylation reaction under Vilsmeier-Haack conditions of the respective pyrazolones **35** (see Schemes 5b and 8a). Consequently, this methodology is another fundamental example of access to halopyrazoles, particularly 5-chloropyrazoles, from ethyl acetoacetate (**68**) as the starting material (Scheme 13b).

2.3.2. Additional Systems

Throughout the entire contribution, several functionalized pyrazole derivatives have been mentioned (i.e., rings substituted with NH_2, CHO, OH, CF_3, SR, CN, CO_2R, Cl, Br, etc.), and some of them managed to be classified within a particular section due to their recurrence (pyrazoles bearing amino or acyl groups); however, there are examples on other functional pyrazoles that are not part of such sections; therefore, in the last section of this chapter, seven works on different or highly functionalized pyrazoles are discussed.

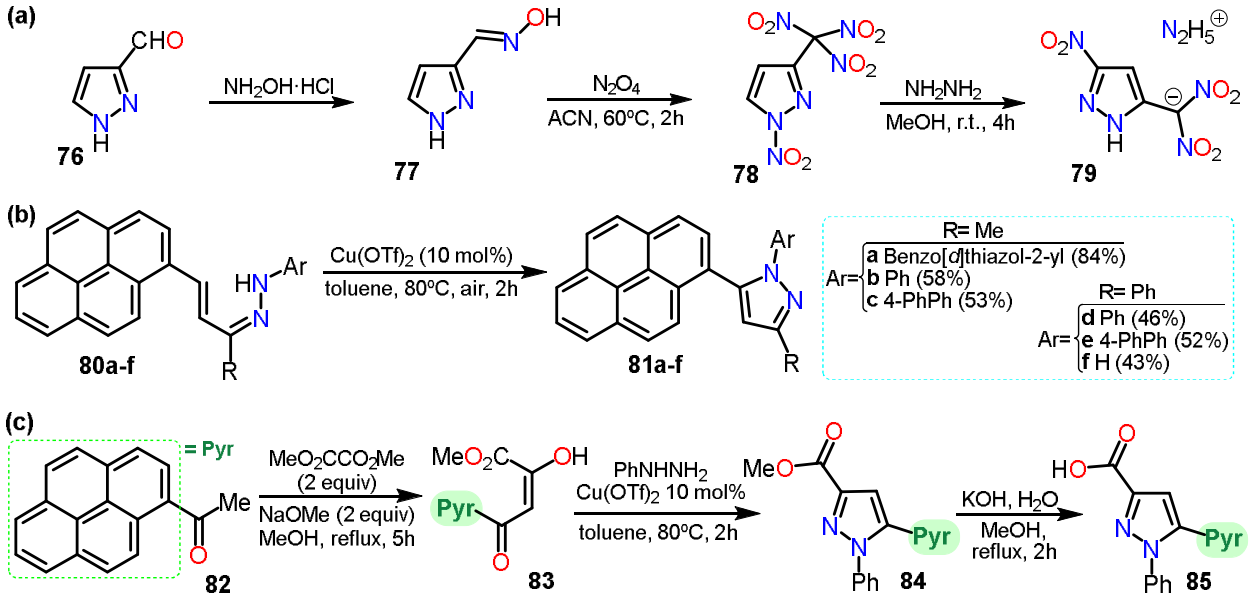
In the first example, Fricero et al. [49] reported the regioselective condensation between ynone-trifluoroborates **69a–e** and hydrazine derivatives to obtain pyrazole 5-trifluoroborates **70** (Scheme 14a). The reaction generates a nitrile intermediate just such as the ones studied in Section 2.1. In this case, products are stable, allowing a chemoselective halogenation of **70** to obtain the fully functionalized pyrazoles **71a–t**. The halogenation methodology is such as the ones mentioned in the above section, using N-halosuccinimides and shows that the halogenation is compatible with the trifluoroborate systems as it does not undergo halodeborylations.

On the other hand, Wei and co-workers [50] reported the synthesis of trifluoromethylated pyrazoles **75a–c**; these pyrazoles were obtained via a double hydroamination reaction of β-CF_3-1,3-enyne **72** with hydrazine derivative **73a–c** (Scheme 14b). First, reagents **72** and **73** undergo an intermolecular hydroamination generating intermediate **74**, in which amine performs a nucleophilic attack over the central sp-carbon to obtain the cyclization products; it is to notice that product **75a** was obtained alongside pyrazolidine which is the non-aromatized product. When **73c** was used, pyrazolidine was obtained, but as it was air sensitive, it was readily oxidized into pyrazole **75c**.



Scheme 14. Synthesis of pyrazoles from (**a**) ynone trifluoroborates and (**b**) from 1,3-enynes.

Another example is the preparation of nitro-substituted pyrazoles. Zhang et al. [51] synthesized 1-nitro-3-trinitromethylpyrazole (**78**) from 3-formylpyrazole (**76**) (Scheme 15a). Compound **78** was used to obtain hydrazinium 5-nitro-3-dinitromethyl-2*H*-pyrazole **79**. The synthetical route, **76** was treated with hydroxylamine hydrochloride to yield compound **77**. Subsequently, **77** was treated with N_2O_4 to obtain **78**, which reacted with hydrazine to obtain the dinitromethylide salt **79**. In this case, in the process of dinitration, C5 was nitrated, too, making it clear that isomerization of *N*-nitropyrazole was carried out during the last step. The isomerization mechanism was elucidated using DFT computational calculations, and the final product was used as an energetic salt.

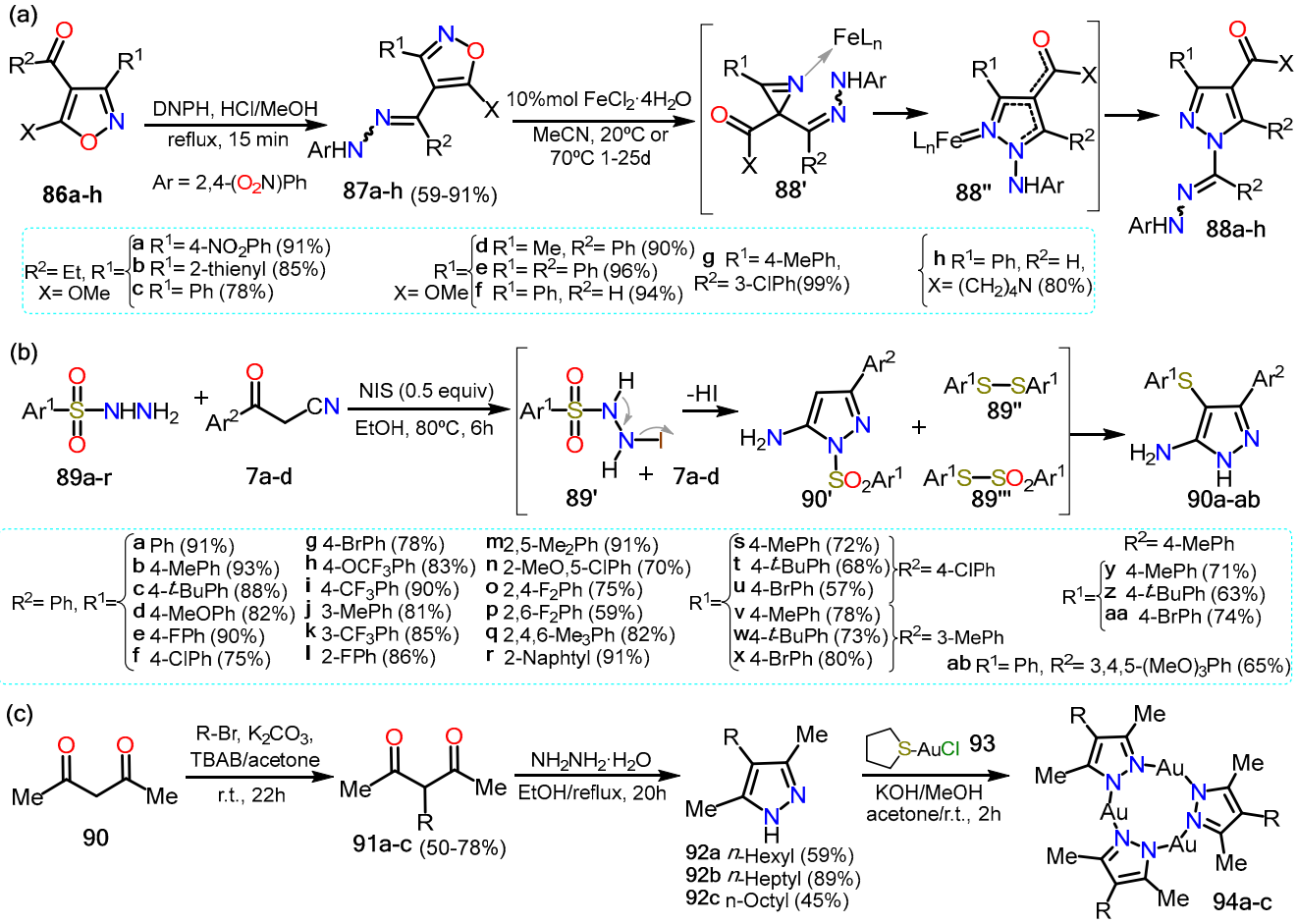


Scheme 15. (**a**) Synthesis of nitro pyrazoles and of pyrene-pyrazoles (**b**) **81** and (**c**) **85**.

Continuing, Sar et al. [52] reported the synthesis of seven pyrene-pyrazole pharmacophores for targeting microtubules (Scheme 15b,c). The pyrenyl-substituted pyrazoles **81a–f** were prepared with the corresponding hydrazones **80a–f** and had side-chain modifications at N-1 and C-3 positions, inserted from the alkenyl hydrazones via C-N dehydrogenative cross-coupling using a copper triflate catalyst under aerobic conditions. Furthermore, the reaction of pyrenylacetophenone (**82**) with dimethyloxalate produced molecule **83** that then

undergoes cyclization reaction with phenylhydrazine to produce **84** via C-N bond formation in one pot. Finally, **84** was treated with KOH/MeOH to yield **85**.

The following two examples imply the amino or the keto group, and their preparation involves analog functional groups to the ones mentioned in the previous sections; though, we mention them since they are highly functionalized compounds. In this context, Galenko et al. [53] synthesized 1-aminopyrazole-4-carboxylic acids using an iron II catalyst (Scheme 16a). The synthesis starts with the isoxazoles **86a–h**, which react with 2,4-dinitrophenylhydrazine (DNPH) to generate both *E*/*Z* isomers of 4-hydrazonomethylisoxazoles **87a–h**. Afterward, the catalyst $FeCl_2 \cdot H_2O$ is added with dry acetonitrile developing a domino rearrangement of the isoxazole via the formation of aziridine intermediate **87′**. The mechanism starts with forming a Fe-isoxazole complex, followed by the ring's opening via N–O bond cleavage to form a Fe-nitrene complex; this complex then undergoes recyclization to form the Fe-azirine complex **87′**. The three-membered ring is open, generating another Fe-nitrene complex that allows the 1,5-cyclization producing the complex Fe-*N*-aminopyrazole **87″**. Lastly, cleavage of the catalyst affords pyrazoles **88a–h** in high yields. Notably, the yields shown are obtained starting from the *E* isomer of the isoxazoles, although the reaction proceeds smoothly for both isomers.



Scheme 16. Synthesis of (**a**) pyrazoles **88**, (**b**) aminopyrazoles **90** and (**c**) trinuclear complexes **94**.

Later, Wei et al. [54] reported a three-component reaction of aroylacetonitriles **7a–x** with arylsulfonyl hydrazides **89a–r** to form 5-amino-4-arylthio-3-aryl-1*H*-pyrazoles (Scheme 16b). The reaction could afford 1-*H* or 1-SO_2Ph products, but in the presence of NIS, the reaction became selective to the 1*H*-pyrazole. Various substituents in arylsulfonyl hydrazides and the β-ketonitrile were tested to investigate the scope of the reaction; it was found that the electronic effects of the aryl group did not influence the reaction. The mechanism reaction proceeds via sequential cyclization and sulfenylation reactions under NIS catalysis. The

reaction starts with the reduction of **89′** that after losing HI and N_2, affording two disulfide spices; that is, 1,2-diphenyldisulfane **89′′** and S-phenylbenzenesulfonothioate **89′′′**. Meanwhile, **7** reacts with **89** via a cyclization reaction to generate the desired 5-amino-1-arylthio-3-arylpyrazole **7′**. Two routes are possible to afford the final products. In the first one, **7′** undergoes electrophilic substitution with **89** to afford the arylthio group at position 4; this product treated with NIS provides the desired aminopyrazoles **90a–ab**. In the other proposed route, **7′** then loses the arylthio group in the presence of NIS and reacts with **89** to afford **90a–ab** which possesses the thioether group at position 4.

To finish, Tsutsumi et al. [55] reported phosphorescent trinuclear Au(I) complexes using *NH*-pyrazoles as ligands (Scheme 16c). Pyrazole is prepared from 2,4-pentanedione (**90**), which is alkylated using K_2CO_3 as a base and an alkyl bromide to afford the α-substituted β-diketones **91a–c**. Afterward, **91a–c** undergoes a cyclization reaction with hydrazine to afford the pyrazoles **92a–c** that then were used to prepare the trinuclear complexes **94a–c** with tetrahydrothiophene-AuCl (**93**). Complexes **94** were recrystallized, and all the crystals exhibited broad unstructured luminescence around 730 nm with quantum yields of 75%, 61%, and 63%, respectively. The complexes did not reveal a good luminescence in diluted solutions; however, the isolated molecules exhibited the opposite behavior, indicating that the formation of aggregates induces the luminescence of the complexes.

3. Applications in Fused Systems

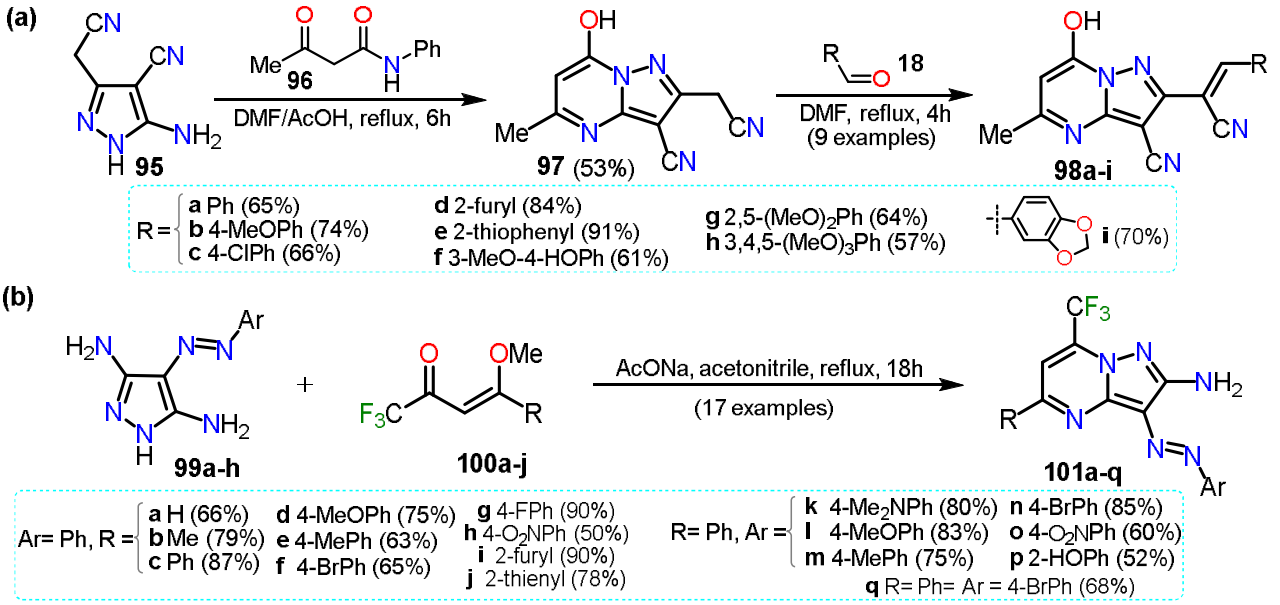
Similar to the pyrazoles, the fused pyrazoles have a wide range of applicability in diverse fields, which has led to several of their derivatives being applied in pharmaceutical, agricultural, biological, physical-chemical, and industrial fields. Thus, the synthetical transformations involving this class of heterocyclic systems have been and will continue to be a research area of extensive interest in various researcher groups. Within the large number of structures that these heterocyclic systems possess, those with a pyrazole nucleus fused to six-membered aromatic rings predominate; indeed, there is a diversity of combinations involving bicyclic, tricyclic, tetracyclic systems, etc; however, the bicyclic systems serve as a reference to know the properties of the other heteroaromatic fused systems, in which only those containing nitrogen atoms as heteroatom are predominant [5,21,24,56,57].

Except for indazoles, the synthetical approaches to access 5:6 fused *N*-heterocyclic systems are mainly based on constructing the six-membered nitrogenous ring, starting from the appropriate pyrazole derivative [5,56,57]. In this section, the syntheses of some representative *aza*-heteroaromatic products are described; that is, pyrazolo[1,5-*a*]pyrimidines, pyrazolo[3,4-*b*]pyridines, indazoles, and the least recurrent pyrazolo[3,4-*d*]pyrimidines, pyrazolo[4,3-*d*]pyrimidines, and pyrazolo[1,5-*a*][1,3,5]triazine rings. Likewise, syntheses of other scarce rings such as imidazo[1,2-*b*]pyrazole and pyrazolo[3,4-*b*]azepine are also discussed. The pyrazolo[1,5-*a*]pyrimidine ring is perhaps the most frequently studied fused-pyrazole due to its applicability and synthetical versatility. Therefore, several specialized reviews on this type of ring have been described in recent years [6]; indeed, more of our recent investigations are pyrazolo[1,5-*a*]pyrimidines-based [6,19].

3.1. Pyrazolo[1,5-a]pyrimidines

The pyrazolo[1,5-*a*]pyrimidine (PP) ring is a heteroaromatic system that admits structural variations in the periphery during ring construction and via later functionalization steps. 5-Aminopyrazoles have been widely studied as 1,3-bis-nucleophilic reactants in cyclocondensation reactions with 1,3-bis-electrophiles such as β-dicarbonyl compounds, β-ketonitriles, β-enaminones, etc. [5,6]. For example, in 2019, Metwally and co-workers [58] synthesized the functionalized pyrazolo[1,5-*a*]pyrimidine **97** through the cyclocondensation reaction between the 5-aminopyrazole derivative **95** with acetoacetanilide (**96**). Then, the Knoevenagel reaction of **97** with various aldehydes **18** led to forming a family of the acrylonitriles **98a–i** in good yields (Scheme 17a). Compounds **97**, **98a**, and **98b** exhibited higher cytotoxicity (doxorubicin is the control) and inhibitory activity against histone lysine demethylases (KDMs); while the 4-chlorophenylidene derivative gave the lowest cytotoxic

activity. Notably, **98a** is the most active KDM inhibitor showing a total apoptotic effect of 10 folds more than the control. The authors presume these results are due to the π–π interactions between the heteroaromatic moieties and the enzyme active site.

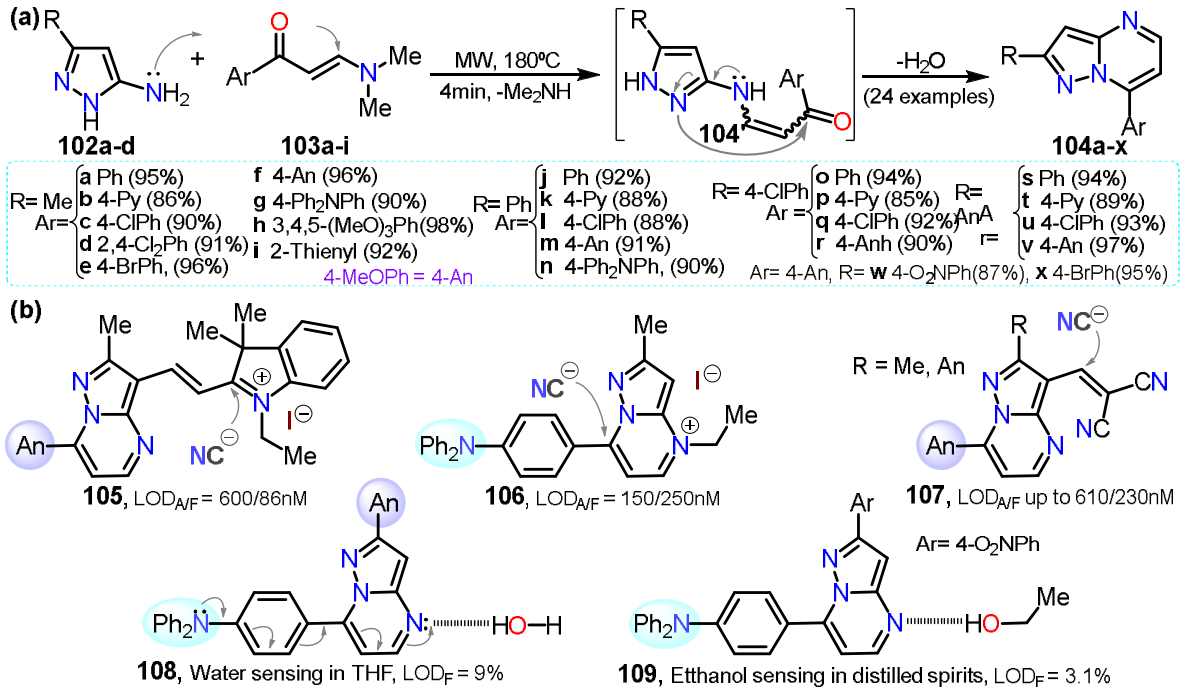


Scheme 17. Synthesis of PPs from (**a**)acetoacetanilide (**96**) and (**b**) 1,1,1-trifluoro-3-buten-2-ones.

Recently, Stefanello et al. [59] carried out the regioselective synthesis of 7-(trifluoromethyl)-3-(aryldiazenyl)pyrazolo[1,5-*a*]pyrimidin-2-amines **101a–q** in 50–90% yields by the cyclocondensation reaction in acetonitrile of 4-(aryldiazenyl)pyrazol-3,5-diamines **99a–g** with substituted 4-methoxy-1,1,1-trifluoro-3-buten-2-ones **100a–j** (Scheme 17b). Due to the verified photophysical properties of pyrazole derivatives [16,19], the authors evaluated these properties in the products. In this context, absorption and emission spectra of **101a–q** were performed in different polarity solvents. All products presented good absorption in the ultraviolet region, although they had low quantum emission fluorescence yields. The spectral changes vary with the solvent polarity according to the electronic nature of the molecules evaluated in the presence or absence of the diazo group –the authors prepared a similar product without the aryldiazenyl moiety. Likewise, the effects of pH variation on **101a** did not seem to affect its ground state or excited state properties.

In the same line, our group has intensively investigated β-enaminones use as 1,3-electrophilic systems in pyrazolo[1,5-a]pyrimidine synthesis in recent years [24,60,61]. Some products have shown photophysical applications, explicitly developing chemosensors for detecting cyanide [19,62] or water in some organic solvents [63] (Scheme 18).

In particular, we have synthesized various pyrazolo[1,5-*a*]pyrimidines derivatives starting from different β-enaminones, some of which are shown in Scheme 17. In those works, the 7-aryl substituted products **104a–x** were synthesized in high yields via the MW-assisted cyclocondensation reaction of 5-aminopyrazoles **102a–d** with β-enaminones **103a–i** under solvent-free conditions (Scheme 18a) [24,60,61]. Regarding the photophysical usages, some 7-arylpyrazolo[1,5-*a*]pyrimidines **104** have been used as precursors to obtain chemosensors **105–107** to detect CN^- with excellent LODs [19,62]; likewise, the two integrated pyrazolo[1,5-*a*]pyrimidine–triphenylamine systems **108** and **109** were used as a fluorescent indicator for the sensing of water content in organic solvents [63] and the ethanol quantification of distilled spirits [16], respectively (Scheme 18b).



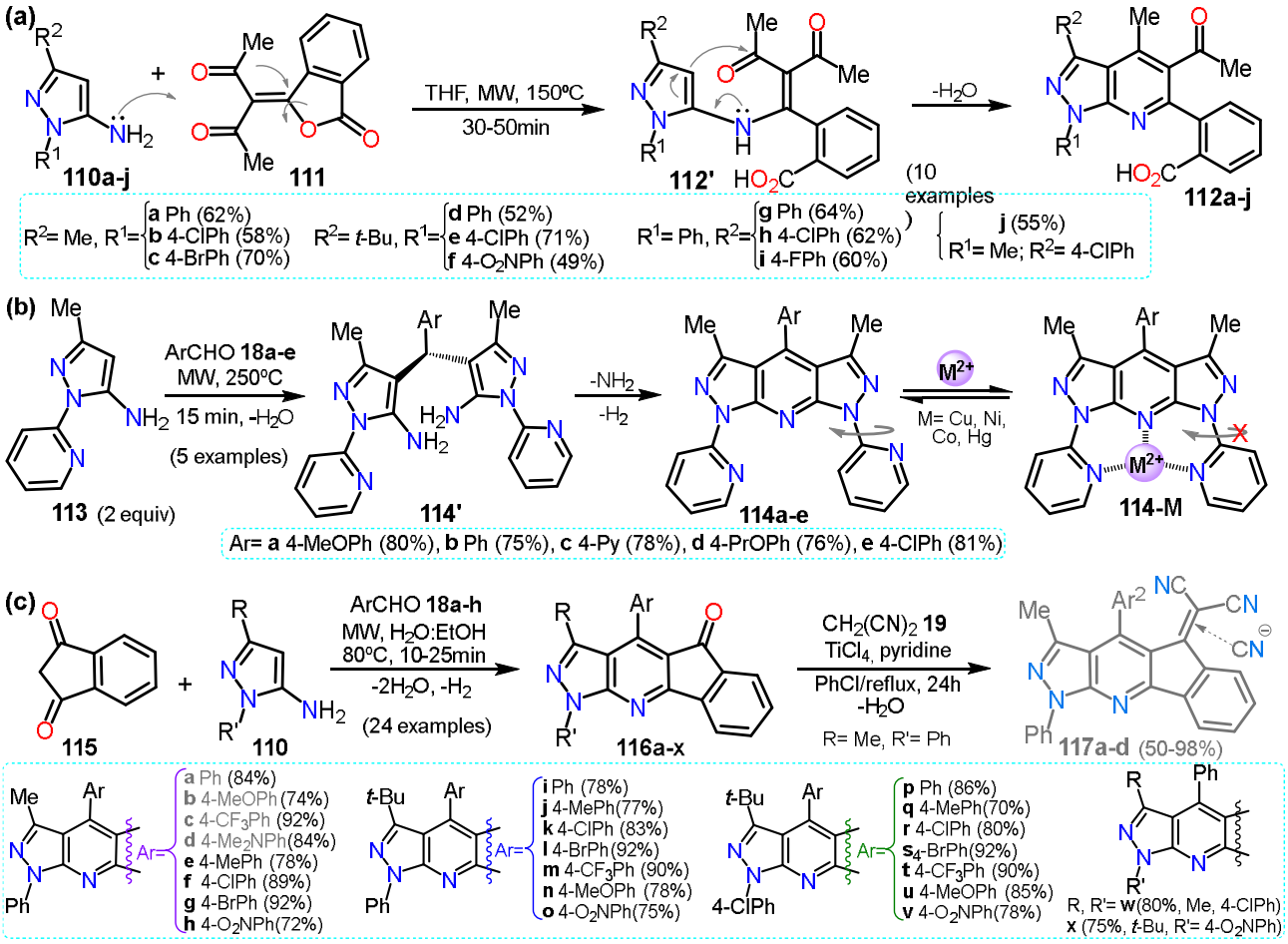
Scheme 18. (**a**) Synthesis of PPs **104** from β-enaminones and their (**b**) photophysical applications.

3.2. Pyrazolo[3,4-b]pyridines

Pyrazolo[3,4-*b*]pyridines (PPys) can be accessed from appropriately functionalized pyridines where the pyrazole ring is formed, or starting from substituted pyrazoles in which the pyridine ring is constructed. In pyrazolo[3,4-*b*]pyridine synthesis is also possible to introduce functional groups during the ring construction or by subsequent functionalization reactions; these processes generally involve the reaction of *N*-substituted 5-aminopyrazoles with 1,3-bis-electrophilic substrates, which can be generated in situ by multicomponent reactions (MCRs) when they are α,β-unsaturated carbonyl compounds generated from arylaldehydes and active methylene compounds such as β-dicarbonyl compounds. When 5-aminopyrazoles unsubstituted at the ring nitrogen atom are used to synthesize PPys, the pyrazolo[1,5-*a*]pyridines formation is mainly observed; however, PPys are favored by using enones 1,3-bis-electrophilic substrates [6,24,64].

In 2017, we reported the MW-assisted regioselective synthesis of fully substituted pyrazolo[3,4-*b*]pyridines **112** through an isobenzofuranone ring-opening reaction from the 1,3-bis-electrophile **111**. *N*-Substituted 5-aminopyrazoles **110** were used in this approach; however, the reaction proceeded by a domino aza-Michael-cyclization-dehydration sequence via the isolated pyrazolyl-enamine intermediate, allowing us to clarify the reaction mechanism involved with the unusual 1,3-biselectrophile **111** (Scheme 19a) [65].

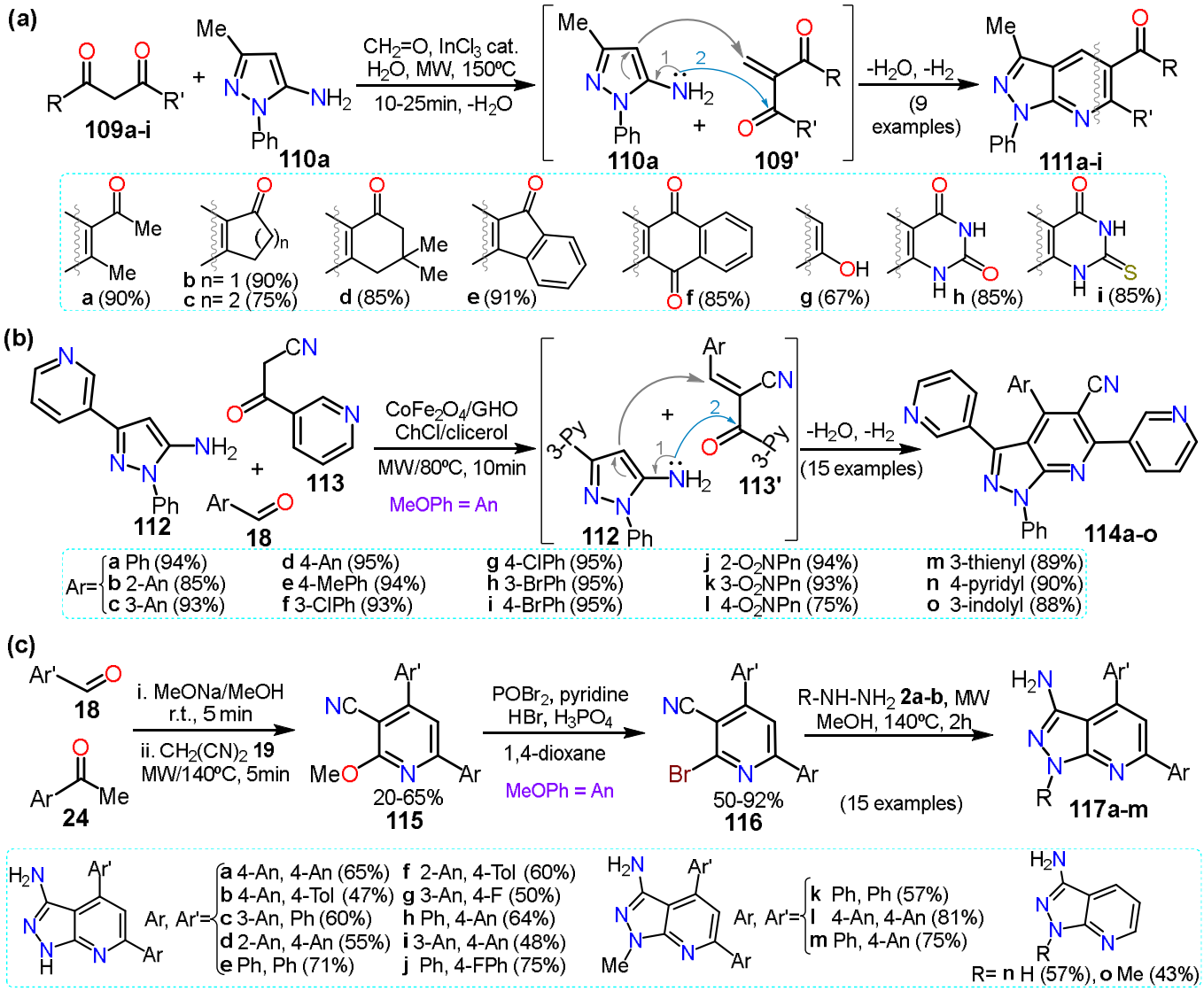
Subsequently, the MW-assisted pseudo-tricomponent synthesis of fluorescent 1,7-dipyridyl-bis-pyrazolo[3,4-*b*:4′,3′-*e*]pyridines **114a–e** was reported for the same group [66]; these fused-pyrazoles were obtained by the reaction of arylaldehydes **18** with two molecules of 5-amino-3-methyl-1-(2-pyridyl)pyrazole (**113**). Tricyclic products **114a–e** were obtained in high yields, and they were used as turn-off reversible chemosensors for nanomolar detection of metal ions such as Cu^{2+}, Co^{2+}, Ni^{2+}, and Hg^{2+}, through the complexes formation **114-M** (Scheme 19c). In our last example on PPys synthesis, indeno[1,2-*b*]pyrazolo[4,3-*e*]pyridines **116a–x** were obtained in high yields by MCRs between arylaldehydes **18**, indan-1,3-dione (**115**), and 5-amino-*N*-arylpyrazoles **110.** Products **116a–x** are 4-azafluorenone systems that, combined with malononitrile (**19**), produced the dicyanovinylidene derivatives **117** bearing different acceptor or donor aryl groups at position 4 (Scheme 19c). The final products were preliminarily studied to detect CN^-, and photophysical and computational studies confirmed an intramolecular charge transfer (ICT) phenomenon [64].



Scheme 19. MW-assisted synthesis of pyrazolo[3,4-*b*]pyridine derivatives (**a**) **112**, (**b**) **114**, and (**c**) **116**.

The last two examples correspond to MW-assisted MCRs, in which the 1,3-bis-electrophilic reagent is in situ generated from an active methylene compound and an aldehyde molecule via a condensation reaction [64,66]. In this context, Gutiérrez et al. [67] developed the MCR of 5-amino-1-phenyl-3-methylpyrazole (**110a**), formaldehyde, and β-diketones **109** in water using $InCl_3$ as a catalyst; this MW-assisted reaction produces pyrazolo[3,4-*b*]pyridine derivatives **111a–i** in high yields (Scheme 20a).

Similarly, Bhuyan et al. [68] carried out the MW-assisted multicomponent reaction between 5-amino-1-phenyl-3-(3-pyridyl)pyrazole (**112**), hetaroylacetonitrile **113**, and arylaldehydes **18** in choline chloride (ChCl)/glycerol; this synthetical approach allows to obtain 1,3,4,6-tetraaryl-5-cyanopyrazolo[3,4-*b*]pyridines **114a–o** in high yields and short reactions times by using sulfonic acid nanoparticles anchored by graphene oxide (G) a catalyst system (Scheme 20b). On the other hand, as a different and unusual example, Cajal and co-workers [69] recently synthesized 6-amino-4,6-diarylpyrazolo[3,4-*b*]pyridines **117a–m** by constructing the pyrazole using hydrazine derivatives **2a–b**, on the preformed and functionalized pyridines **116** (Scheme 20c). The final products were obtained in moderate to good yields under microwave conditions, such as the preparation of intermediates **115** were obtained starting from strategically substituted acetophenones **24** and arylaldehydes **18**; it is important to note that the authors carried out a rational design to identify and validate the 4,6-diaryl-pyrazolo[3,4-*b*]pyridin-3-amine scaffold as the core for mitogen-activated protein kinases (MAPKs) inhibitors; they concluded that aryl groups at positions 4 and 6 of the fused ring are essential for the activity of the compounds.



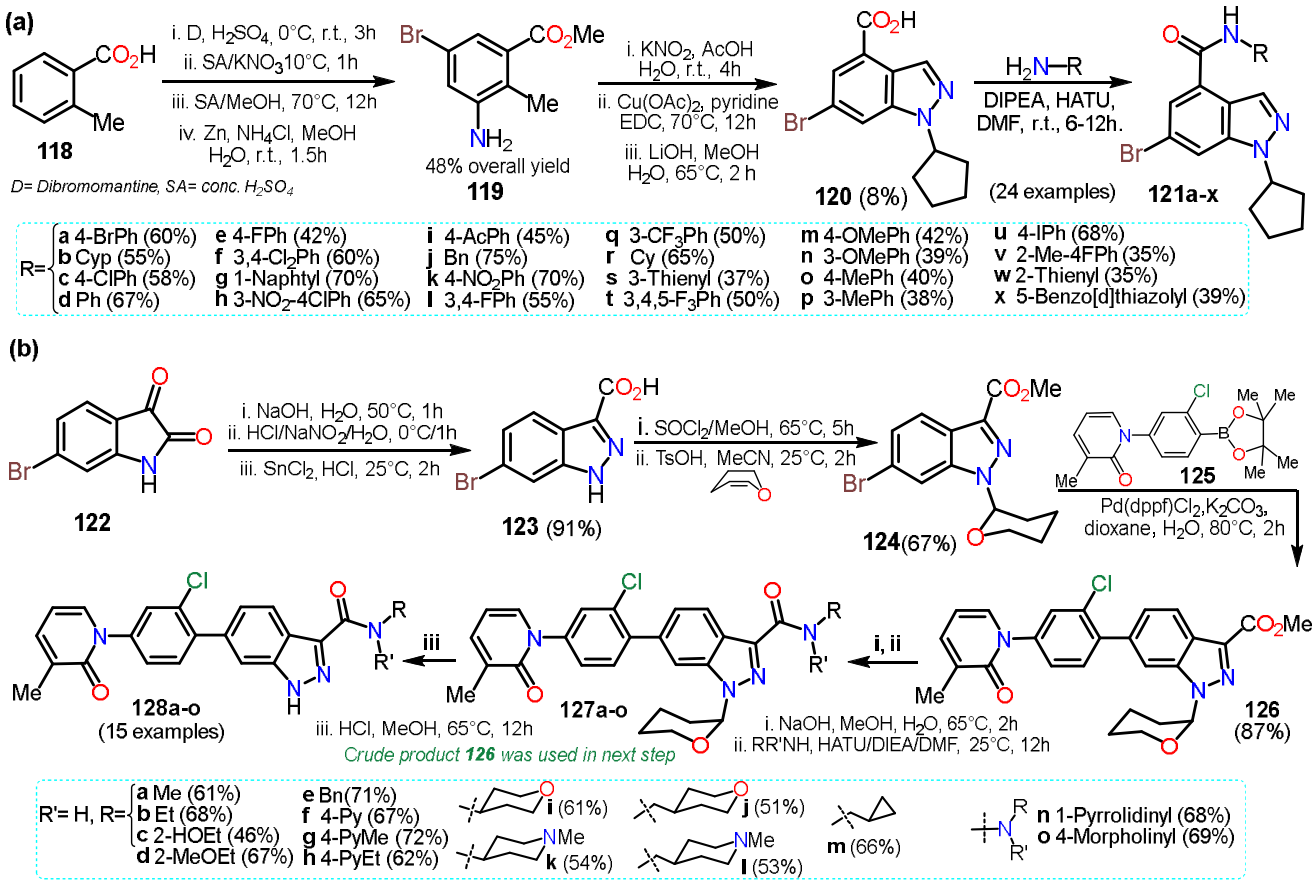
Scheme 20. MW-assisted synthesis of PPys (**a**) **111** and (**b**) **114**. (**c**) Synthesis of PPys **117**.

3.3. Indazoles and Other Bicyclic Pyrazole-Based

Similar to pyrazolo[1,5-*a*]pyrimidine, indazole is another recurrent bicyclic ring type containing pyrazole; this one is a benzo-fused system with two possible tautomeric forms (1*H*- and 2*H*-), in which the 1*H*-indazole tautomer is the most stable and predominant form. Different indazoles possess significant pharmacological activities and serve as structural motifs in drug molecules. Thus, various approaches have been developed to obtain indazole derivatives, and some specialized reviews have been published on this scaffold's synthetical and biological properties. The indazole ring construction is usually accessed from appropriately functionalized benzene derivatives, on which the pyrazole ring is formed. In this context, two representative examples are shown below [56,70,71].

First, Sawant et al. [70] synthesized a series of amides indazole-substituted **121a–x**, which were evaluated for anticancer, antiangiogenic, and antioxidant activities; moreover, the potential to inhibit the pro-angiogenic cytokines associated with tumor growth of indazole derivatives **121a–x** was evaluated finding quite promising results (Scheme 21a). Indazole derivatives **121a–x** were obtained in eight steps starting from 2-methylbenzoic acid (**118**), which was brominated, nitrated, esterified with methanol, and then reduced in the presence of zinc to obtain the aminoester **119**. With the aniline derivative **119**, a cyclization was carried out to form the benzo-fused pyrazole, which was subjected to

coupling and hydrolysis reactions to obtain the *N*-substituted indazole **120**. Finally, the carboxylic acid **120** reacted with different primary amines to yield **121a–x**.

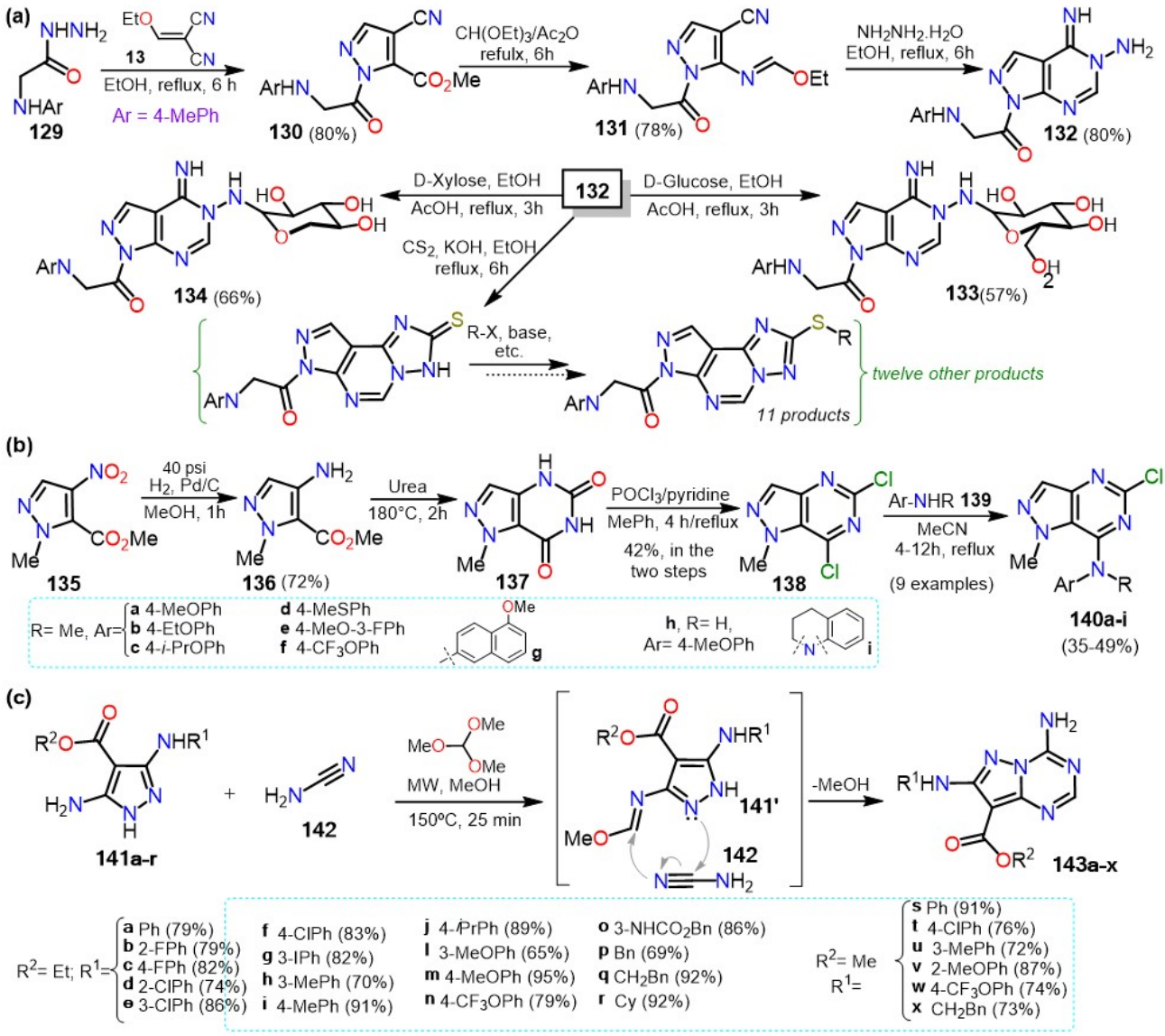


Scheme 21. Synthesis and functionalization of indazole derivatives (**a**) **120** and (**b**) **123**.

On the other hand, Zhang et al. [71] obtained potential p21-activated kinase type 1 (PAK1) inhibitors with kinase selectivity 1*H*-indazole-3-carboxamides-based. First, the THP-protected (THP = 2-tetrahydropyranyl) methyl indazole-3-carboxylate **125** was obtained from the commercial 6-bromoindoline-2,3-dione (**122**), which was subjected to cleavage in basic media, diazotization and finally the reduction and cyclization of the diazonium salts previously created to yield **123**. Compound **123** was esterified and then converted to the THP-protected **124** and subjected to a Suzuki reaction with **125** to afford the coupling product **126**. Then, a conversion to the respective amide **127a–o** via hydrolysis of **126** and amide coupling reactions was developed (Scheme 21b). Finally, THP deprotection afforded the final products **128a–o**. Indazole **124** and other intermediates were used to obtain products similar to **128**, and their biological activities were tested.

Below are three examples of other 5:6 fused rings that are less recurrent but equally relevant in the biological properties of their derivatives; these are pyrazolo[3,4-*d*]pyrimidine [72], pyrazolo[4,3-*d*]pyrimidine [73], and pyrazolo[1,5-*a*][1,3,5]triazine rings [74]; remember that the second core is part of the famous Viagra (sildenafil) [12]. The pyrimidine or 1,2,5-triazine rings are constructed on the appropriate pyrazole derivatives in the three presented examples [72–74]. In this context, Nassar and co-workers [72] obtained the pyrazolo[3,4-*d*]pyrimidine derivative **132**, as a strategic intermediate, starting from 2-(*p*-tolylamino)acetohydrazide (**129**). The reaction of **132** with D-glucose and D-xylose, in the presence of a catalytic amount of acetic acid, afforded the amino-sugar products **133** and **134**, respectively. Products **132–134** were obtained in high yields (Scheme 22a). Compounds **133**, **134**, and other twelve products, obtained starting from **132** (i.e., ten pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines and the two thioglycosides), were designed as novel

cyclin-dependent kinases type 2 (CDK2) targeting drugs. Results revealed these compounds showed superior cytotoxic activities against MCF-7 (IC_{50} of 45–97 nM) and HCT-116 (IC_{50} of 6–99 nM). The growth of the three examined cell lines was significantly inhibited by most of the prepared compounds.



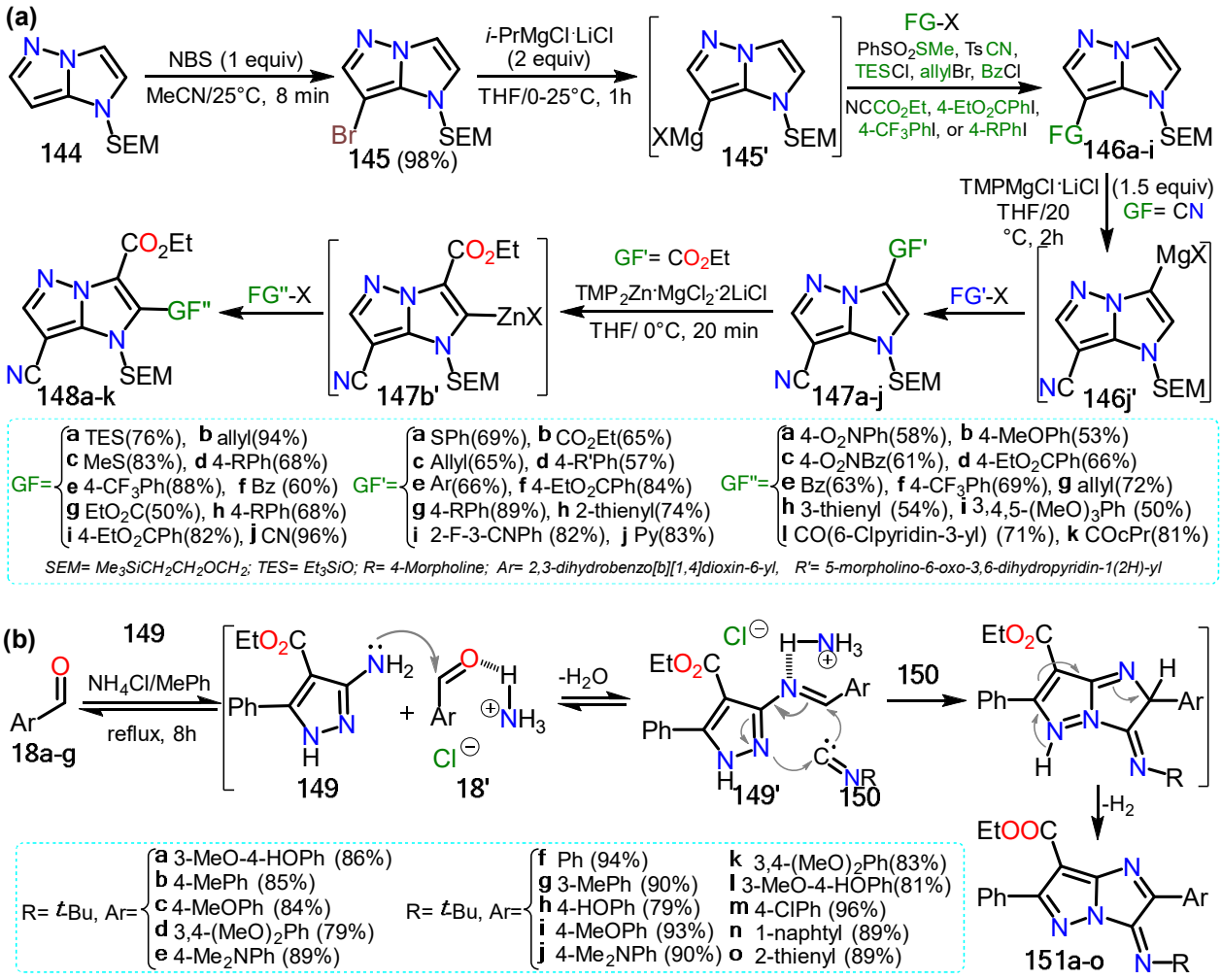
Scheme 22. Synthesis of pyrazolo (**a**) [3,4-*d*]pyrimidines, (**b**) [4,3-*d*]pyrimidines, and (**c**) [1,5-*a*]triazines.

Regarding pyrazolo[4,3-*d*]pyrimidine derivatives, Islam et al. [73] carried out the design, synthesis, and biological evaluation of 7-(*N*-aryl)amino-5-chloro-1-methylaminopyrazolo[4,3-*d*]pyrimidines **140a–I** as inhibitors of tubulin polymerization and colchicine binding. Products **140** were obtained in four steps from the nitrated pyrazole ester **135**, which was reduced to the aminopyrazole **136** and then cyclized with urea to afford the fused pyrazole **137**. Subsequently, **137** was chlorinated under Vilsmeier-Haak conditions forming the dichloro-derivative **138**, which finally suffered a NAS reaction with different aniline derivatives **138** to deliver the final products **139a–I** (Scheme 22b); it should be noted that the authors also prepared the arylamines **138** since these have a specific substitution that is part of the structural design study.

In the last analyzed work of 5:6 fused *N*-heterocyclic systems, Lim et al. [74] reported the multicomponent synthesis of a series of 5-aza-9-deaza analogs of purine using a selective annulation of 1,3,5-triazine ring starting from 4-aminopyrazole-4-carboxylates **141a–r** (Scheme 22c). The mechanism undergoes the creation of an amidine intermediate **141′**,

which then reacts with cyanamide **142** through cyclization reaction to afford the desired pyrazolo[1,5-*a*][1,3,5]. The method was proven practical due to its economy and operational simplicity, short reaction times, good yields, and purity of products.

In the final part of this review, we describe four additional examples that are part of two rings with a fusion of type 5:5 and 5:7. Two of the works correspond to the imidazo[1,2-*b*]pyrazole ring [75,76] and the other ones to the pyrazolo[3,4-*b*]azepine ring [77,78]. In these examples, the 5- or 7-membered ring is built on the respective pyrazole derivative, and, similar to the two previous examples, they are scarce fused rings to find. Regarding imidazo[1,2-*b*]pyrazoles, Schwärzer et al. [75] reported a selective functionalization of the fused ring to obtain products **146–148** (Scheme 23a), beginning with the exchanging Br for Mg (to form **146**) from the SEM-protected fused pyrazole **148** (SEM = trimethylsilylethoxymethyl), and continuing with a regioselective magnesiations (to form **147**) or zinc cation (to form **148**) using TMP-bases (TMP = 2,2,6,6-tetramethylpiperidyl).

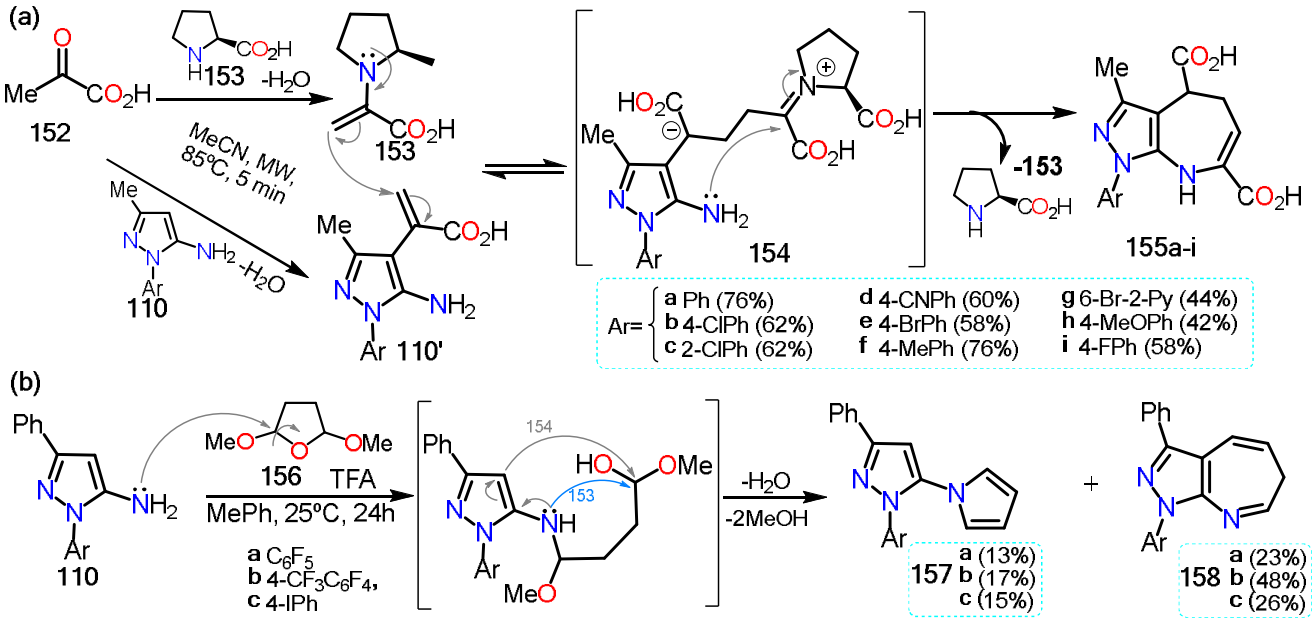


Scheme 23. Synthesis of 1*H*-imidazo[1,2-*b*]pyrazole derivatives (**a**) **145–148** and (**b**) **151**.

Precursor **144** was selectively brominated with NBS producing the 7-bromo substituted derivative **145**, which was used as a substrate in the reaction with *i*-PrMgCl·LiCl, forming the magnesiated intermediate **145′** that then reacts with varios electrophiles (i.e., S-methyl sulfonothioate, tosyl cyanide, and TESCl) and by transmetallations to give **146a–i**. Notably, the authors found that using CuCN·2LiCl or $Pd(PPh_3)_4$ as a catalyst allows the allylation or acylation/arylation on **146j′**, respectively, obtaining crosscoupling products with electron-rich and electron-deficient groups. Products **146a–I** were submitted to a selective magnesiation on C3 using TMPMg·LiCl (via **147b′**), and various reaction conditions

allowed products **148a–j**. The third functionalization on C5 was developed using TMP_2Zn $MgCl_2$·LiCl (via **148′**), and products **148a–k**, after different reactions, were obtained. The pyrazole ring of these compounds was fragmented, accessing to push-pull dyes of which absorption and photoluminescence properties were studied.

In 2020, Peytam et al. [76] reported synthesizing a new series of imidazo[1,2-*b*]pyrazole derivatives **151a–o**, which were tested in vitro to evaluate their α-glucosidase inhibitory activity; these products were prepared via a three-component reaction between arylaldehydes **18**, 3-amino-5-phenyl-1*H*-pyrazole-4-carboxylate **149**, and isonitrile derivatives **150** in the presence of ammonium chloride. Initially, **18** and ammonium chloride form intermediate **18′** during an acid-base equilibrium. Subsequently, this intermediate produces the conjugated iminium salt **149′** through its condensation with the aminopyrazole derivative **149**. To finish, treatment of the iminium salt **149′** with isonitriles **150** affords the heteroaromatic products **151a–o** through a chelotropic reaction (via the carbene-type species **150**) and future oxidation reaction on the adduct **151′** (Scheme 24b).



Scheme 24. Use of 5-aminopyrazoles in synthesizing pyrazolo[3,4-*b*]azepines (**a**) **155** and (**b**) **158**.

On the other side, Quiroga and co-workers [77] reported a new series of pyrazolo[3,4-*b*]azepines **151a–i** via a condensation reaction between 5-aminopyrazoles **101** and pyruvic acid **148** using L-proline (**149**) as a catalyst (Scheme 24a).

The proposed mechanism for the authors starts with substrate **152** reacting with **153** to form the enamine **153′**. At the same time, **110** performs a nucleophilic addition over the carbonyl group of another molecule of **152** with subsequent dehydration and to generate **110′**. Later, **153′** performs β nucleophilic addition over **110′**, rendering intermediate the dipolar **154**. The amino group of **154** performs an intramolecular nucleophilic addition over the iminium carbon followed by a reorganization of the negative charge and elimination of L-proline to obtain the final products **155a–i** in moderate to good yields either under MW irradiation or conventional heating. Notably, three synthesized pyrazolo[3,4-*b*]azepines **155** inhibited *Neisseria gonorrhoeae* growth.

Ultimately, Bortnak et al. [78] reported a series of 5,7-bicyclic framework **158a–c** from 1-perfluoroaryl substituted 5-aminopyrazoles **110** ad 2,5-dimethoxytetrahydrofuran **156** (Scheme 23b). First, the aminopyrazoles **110** the cyclocondensation reaction of the appropriate perfluorinated hydrazine with 3-oxo-3-phenylpropanenitrile (benzoylacetonitrile) **7**. Subsequently, **110** was subjected to Clauson-Kaas reaction in which a mixture of 5-(1-pyrrolyl)pyrazoles **157a–c** and pyrazolo[3,4-*b*]azepines **158a–c** was obtained in moderated yields after separation by flash chromatography using silica gel and ethyl acetate/isohexane

(1:19) as eluent; the major product corresponded to the azepine derivative **158**. Notably, molecular structures of the perfluorinated aminopyrazoles and the two types of bicyclic products were confirmed by single crystal X-ray diffraction.

4. Conclusions

In summary, the literature search on the synthesis and properties of pyrazoles allows us to evidence many works published since 2017 and even from more years ago; however, the investigation regarding pyrazole derivatives in synthetic, biological, and physical-chemical fields remains attractive. Thus, various works should have been left out of our discussion, although we try to cover in the best way the most relevant aspects of the analyzed papers. An acceptable contribution to the synthesis and properties of some pyrazole derivatives was achieved, allowing us to find some generalities summarized below.

Both pyrazoles and their 5:6 fused derivatives are obtained mainly by cyclocondensation reactions using 1,3-biselectrophilic substrates; for example, the reaction with hydrazine derivatives afford pyrazoles, while with 5-aminopyrazoles, pyrazolopyridines or pyrazolopyrimidines are obtained. Usually, reactions are carried out in highly polar solvents under heating, and functionalized products using specific reagents to avoid later reaction steps are obtained; indeed, aminopyrazoles are obtained when the substrate has a nitrile group. Regarding acylpyrazoles, most works are limited to Vilsmeier-Haack reactions on pyrazoles; however, many acyl groups are introduced via the ring construction.

Due to the exceptional synthetical flexibility and electronic properties of pyrazole-containing compounds, different reactions that allow modular structural modifications can be carried out. From these transformations, the biological and photophysical properties of the products can be enhanced, and thus, novel and better applications would be developed by a rational design. Notably, various biologically and photophysically active pyrazole derivatives possess the 4-methoxyphenyl group; the donor nature of this group favors specific interactions in the environment where it acts, as well as internal charge transfer phenomena. Compounds substituted with halogen atoms, such as fluorine or chlorine, have also shown important biological properties.

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