Synthesis and Properties of Pyrazoles

Subjects: Chemistry, Organic

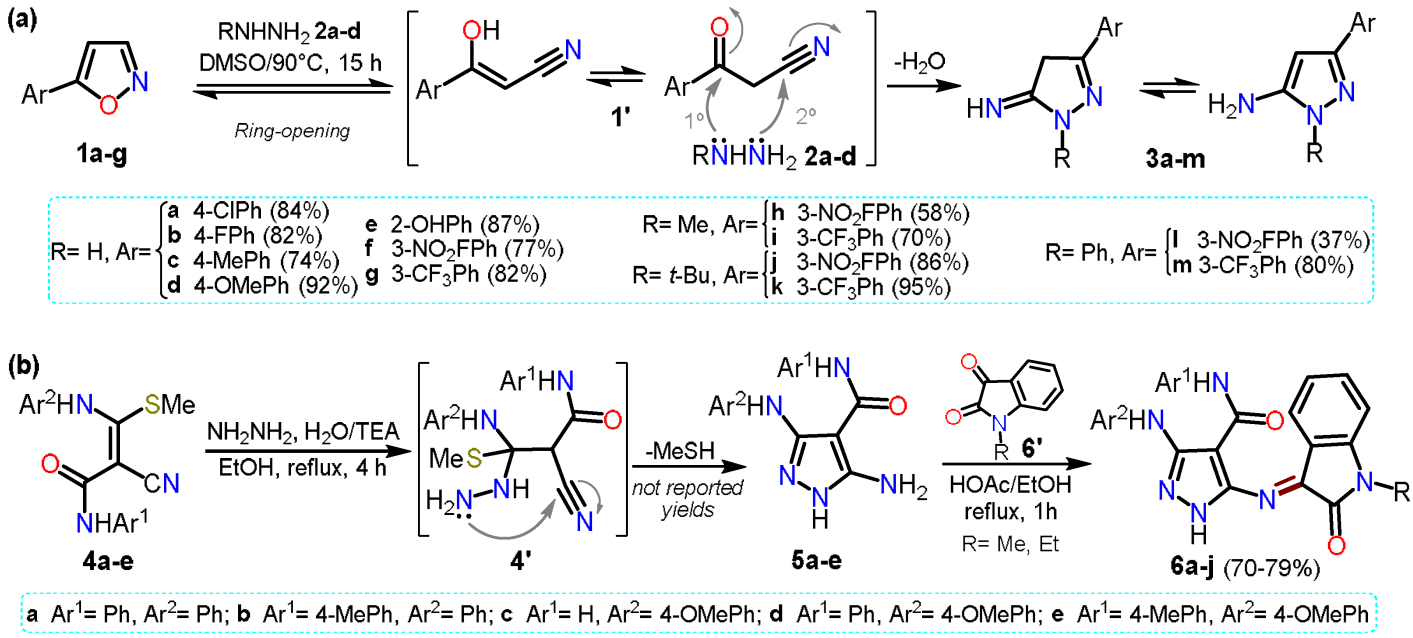
Contributor: María-Camila Ríos , Jaime Portilla

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; 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.

acylpyrazoles aminopyrazoles bioactivities photophysical

1. Aminopyrazoles

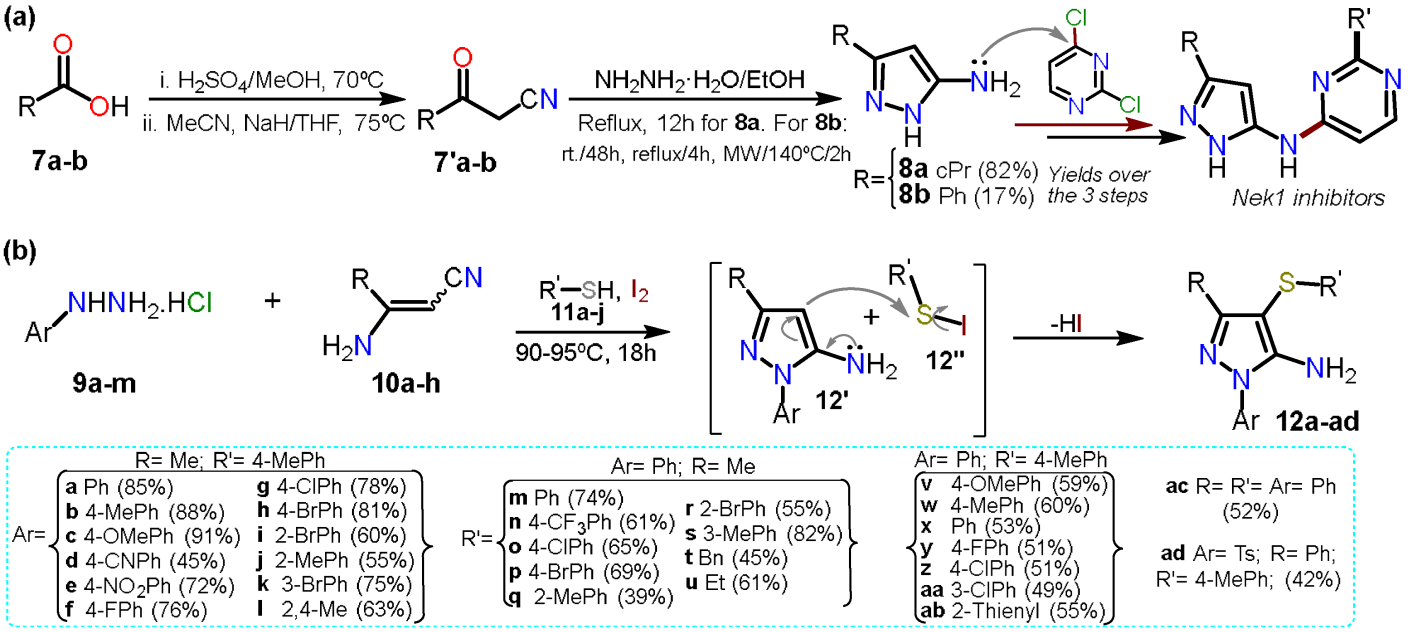
This chapter is strarted by discussing synthetical procedures used to obtain 5-aminopyrazoles, whose chemistry has been well documented for a long time [1][2]. The examples are supposed to be exposed from the last five years; however, other earlier key examples are worth mentioning. For instance, the work reported in 2016 by Kallman et al. [3] will be mentioned, 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 1a).



Scheme 1. Synthesis of 5-aminopyrazoles by (**a**) isoxazole ring-opening and (**b**) from enaminonitriles.

In 2021, Hassan and co-workers [4] 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 1b). 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. Herein, 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.

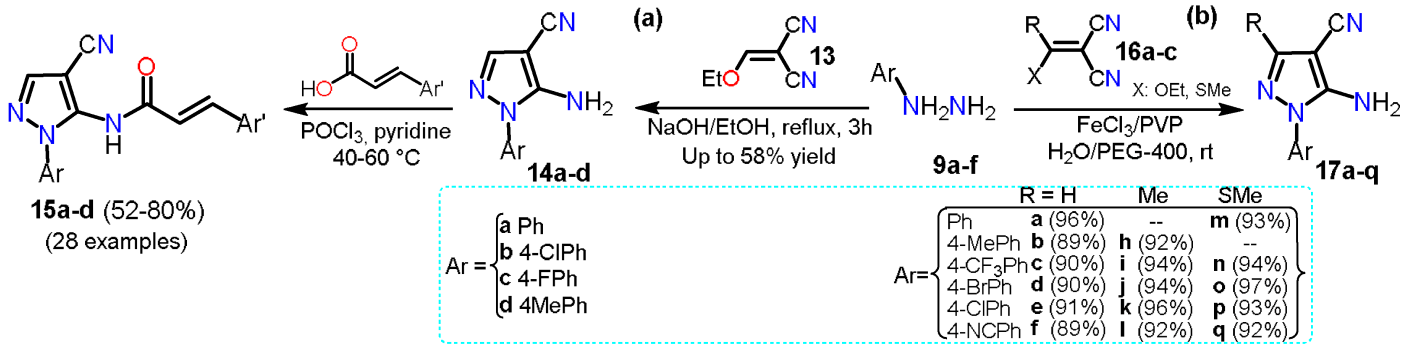
On the other hand, Pilakowski et al. [5] synthesized 5-alkyl-3-amino-1*H*-pyrazoles **8a–b** starting from carboxylic acids **7a–b** (Scheme 2a). First, an esterification reaction was developed, and the respective ester was treated with sodium hydride and acetonitrile to form the corresponding ketonitrile **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 2. 5-Aminopyrazole synthesis forms (**a**) carboxylic acids and (**b**) enaminonitriles.

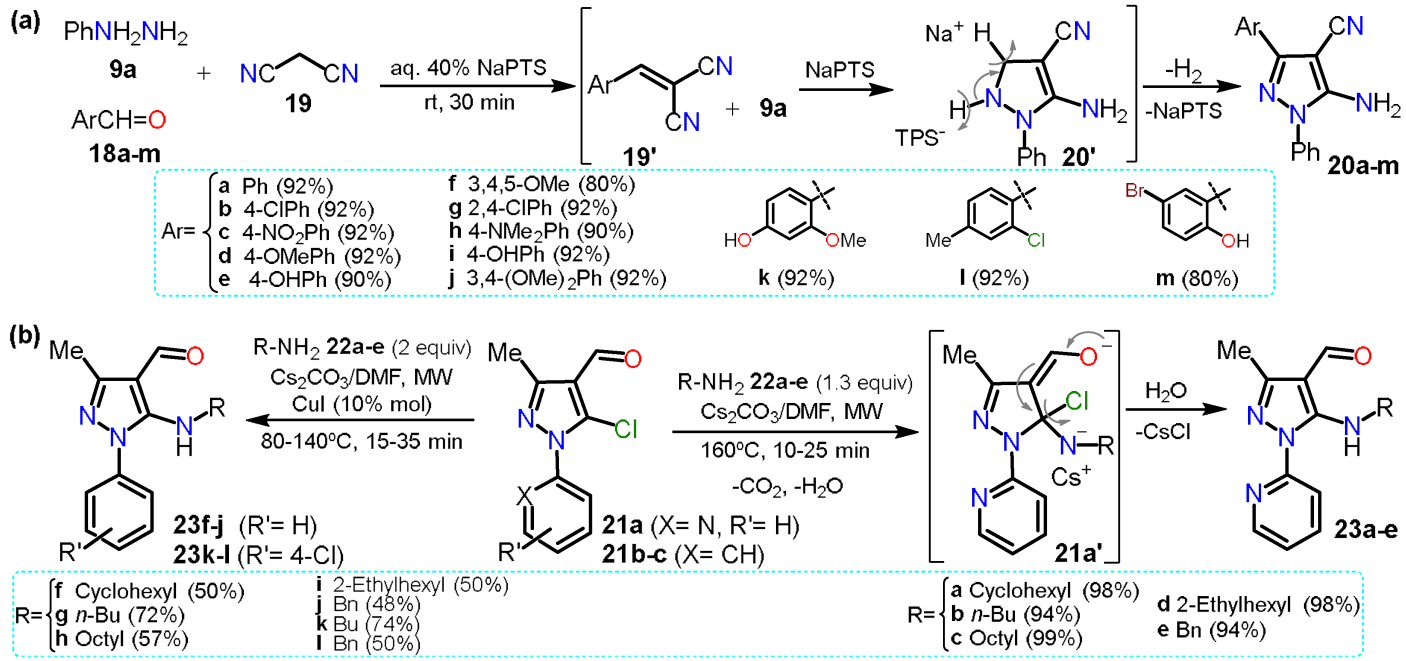
In another recent approach, Annes et al. [6] reported a free-metal and free-solvent multicomponent synthesis mediated by iodine to obtain aminopyrazole-thioether derivatives **12a–ad** in the range of 39–91% yield. The multicomponent reaction comprises substituted hydrazines **9a–m**, nitriles **10a–h** 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 2b); 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. [7] 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 3a). 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 [8] 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 3b).



Scheme 3. Pyrazole synthesis from malononitrile derivatives (**a**) **13** and (**b**) **16a–c**.

In 2020, Sapkal and Kamble [9] 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, it is believed that 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.



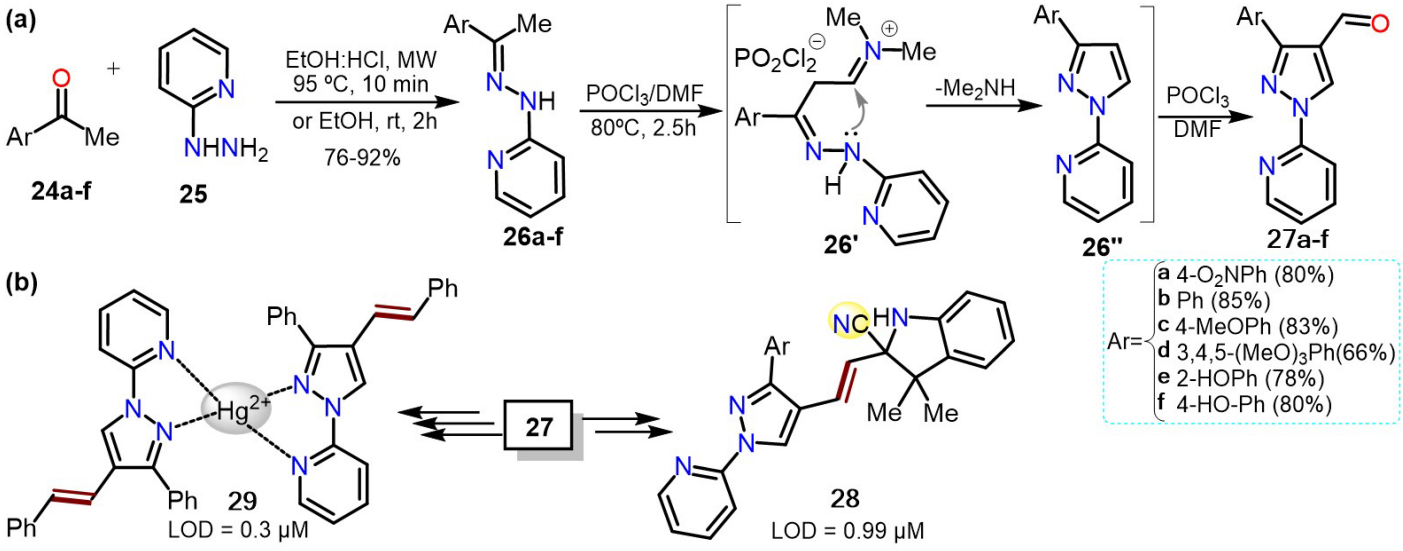
Scheme 4. Synthesis of 5-aminopyrazoles from (**a**) malononitriles and (**b**) 5-chloropyrazoles.

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** [10]. 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 4b).

2. Acylpyrazoles

2.1. Formylpyrazoles

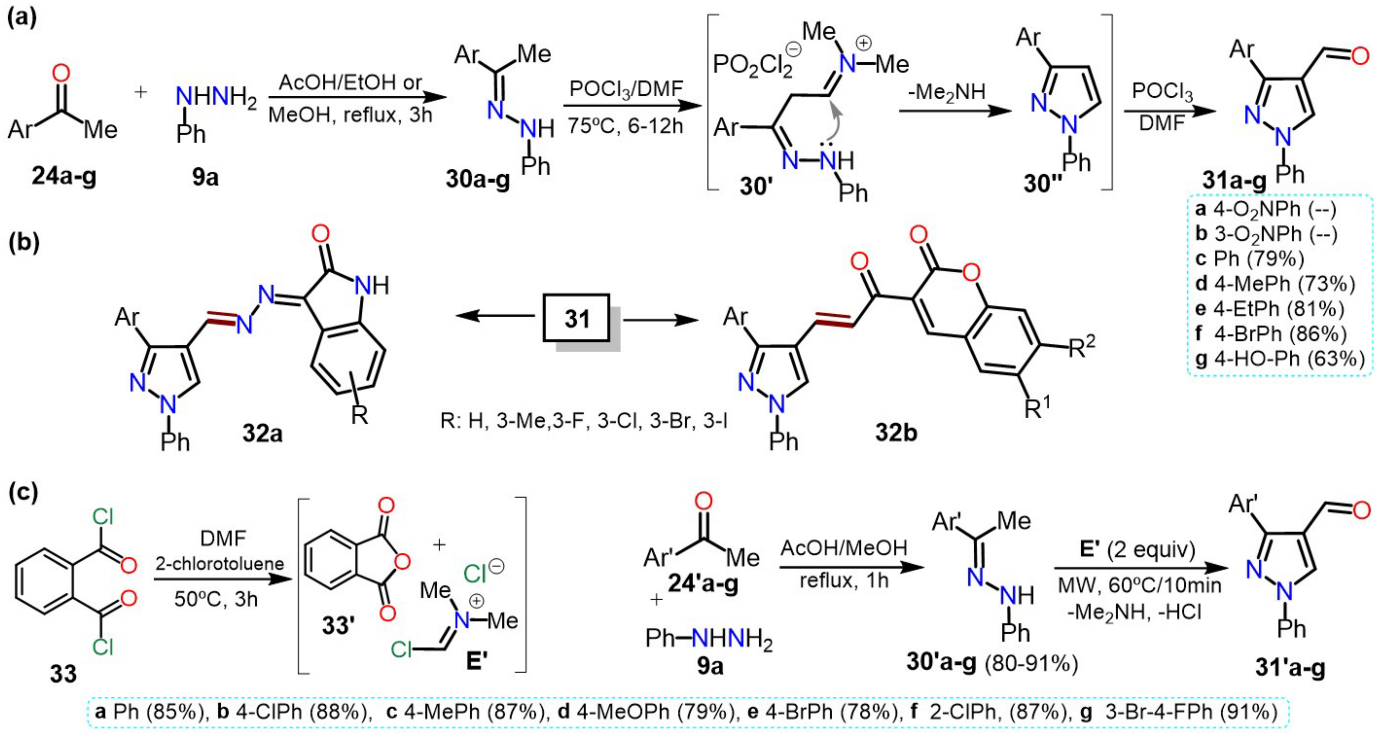
Formylpyrazoles are strategic intermediates in obtaining a wide range of biologically active compounds, with the 4-formyl derivatives being more usual; they possess a high synthetical versatility allowing them a plethora of reactions for the insertion of more functional groups. The research group has 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 5a).



Scheme 5. 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^-) [11][12]; 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 [12]. 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 [13] (Scheme 5b); these LODs values are below the respective limits of the World Health Organization (WHO) [14].

Similarly, Kaur et al. [15] 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 6a). Herein, the yields are not particularly dependent on the different substituents.

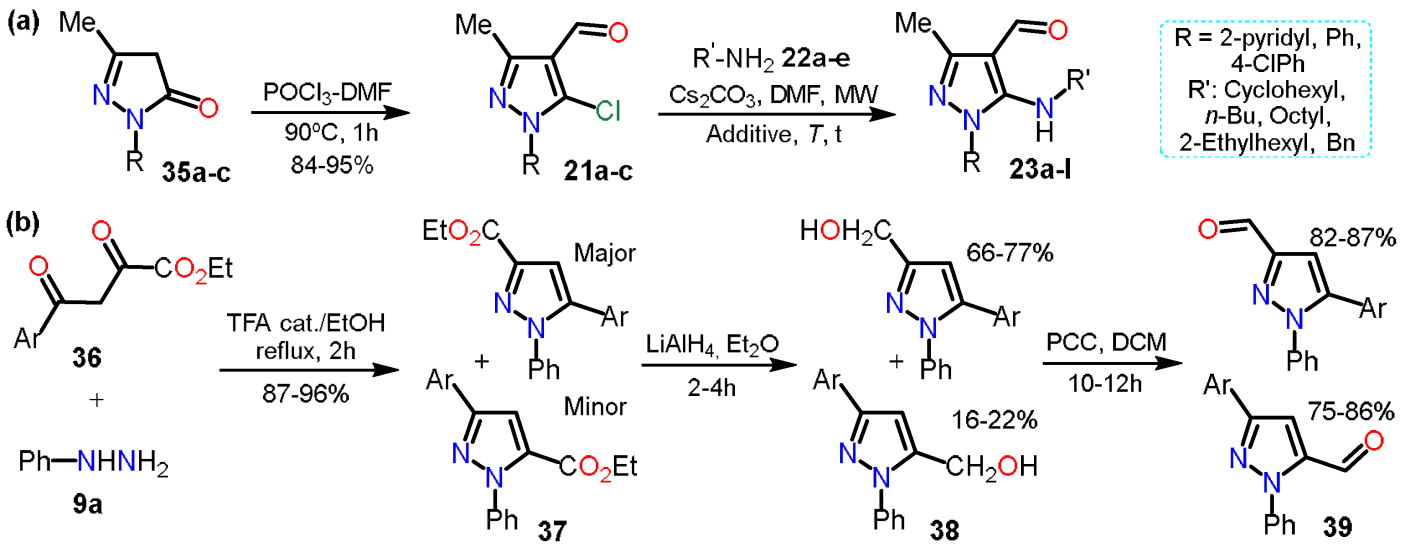


Scheme 6. Synthesis of (**a**) 4-formylpyrazoles and (**b**) biologically activity pyrazoles. (**c**) Reaction de VH using PDC **33**.

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 6b) [16]. 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. [17] 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 7a). In the next synthetic step, chlorine was substituted, generating only the 5-amino-4-formylpyrazoles **23** chemoselectively [10].



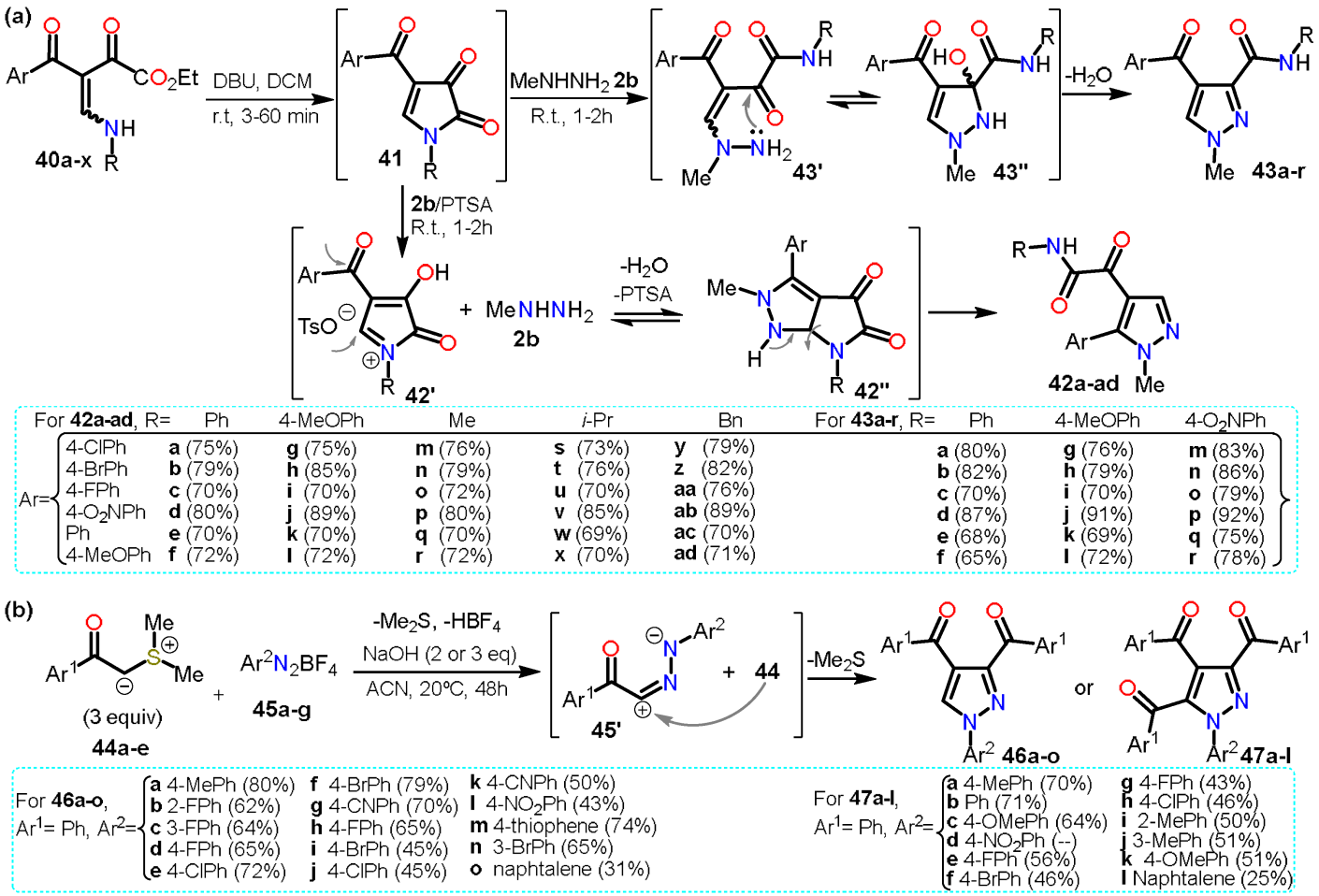
Scheme 7. Synthesis of formylpyrazoles from (**a**) pyrazolones and (**b**) diketoesters.

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 [18][19] that was decided to consider since it is 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 7b).

2.2. Other Acylated Derivatives

Regarding other acylpyrazoles, Poletto et al. [20] 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 8a).

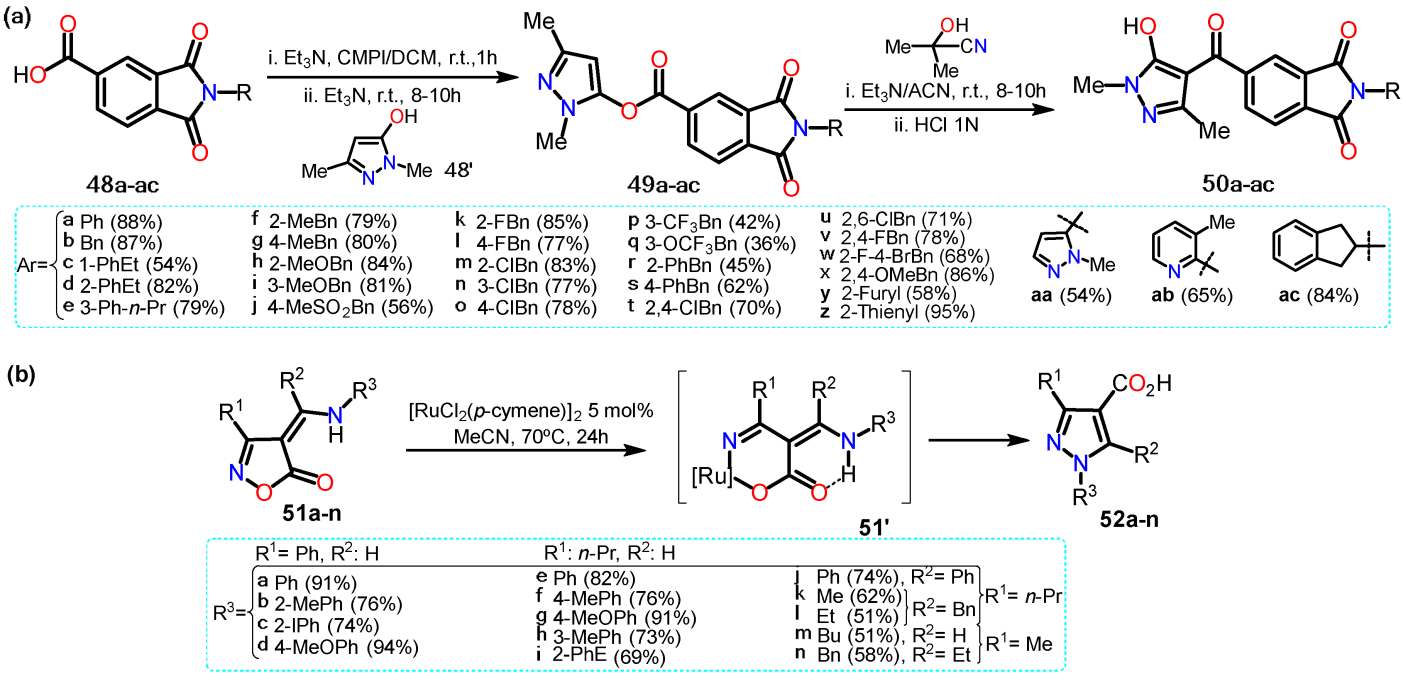


Scheme 8. Synthesis of acylpyrazoles from (**a**) β-enaminodiketones and (**b**) sulfur ylides.

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. [21] 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 8b).

In a different work, He et al. [22] synthesized acylpyrazoles **50a–ac** from N-substituted isoindoline-1,3-dione derivatives **48a–ac** (Scheme 9a). 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 9. Synthesis of acylpyrazoles from (**a**) 1,3-dimethyl-1*H*-pyrazol-5-ol and (**b**) isoxazolones.

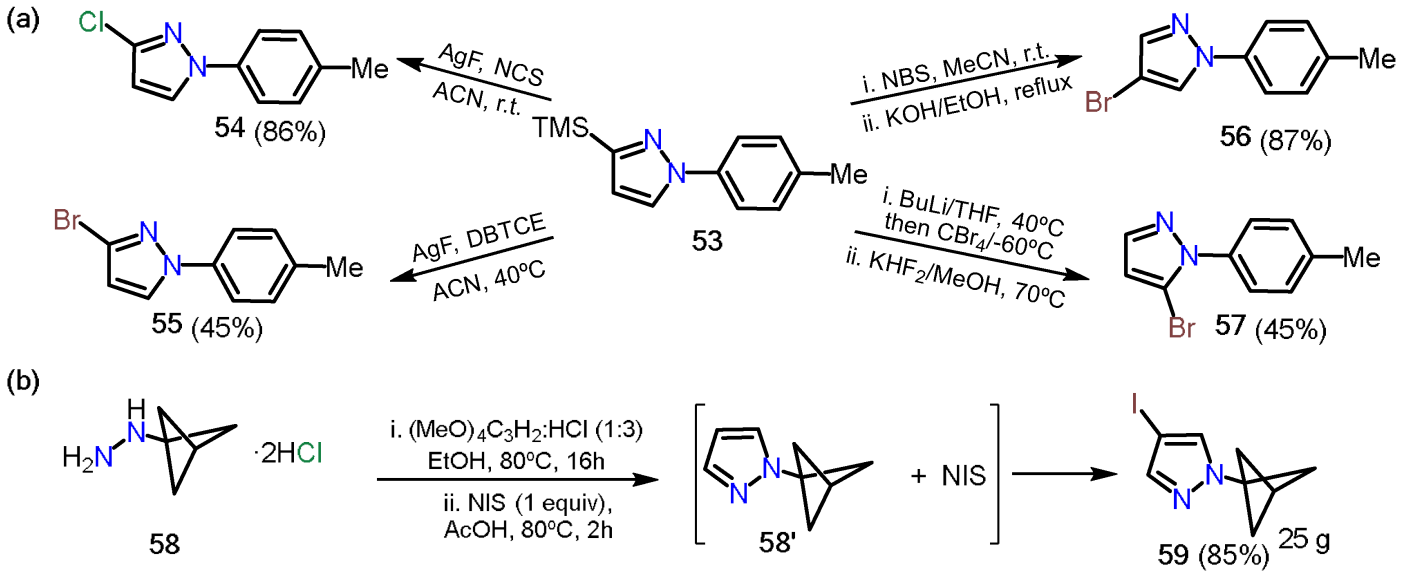
Recently, Loro et al. [23] obtained pyrazole-4-carboxylic acids **52a–n** starting from isoxazole-5(4H)-ones (**51a–n**) using $[RuCl_2(p\text{-cymene})]_2$ as a catalyst. The transformation begins with a ring-opening non-decarboxylative path that generates a vinyl Ru-nitrenoid intermediate that undergoes cyclization to afford the desired pyrazoles (Scheme 9b). 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.

3. Further Functional Pyrazoles

3.1. Halopyrazoles

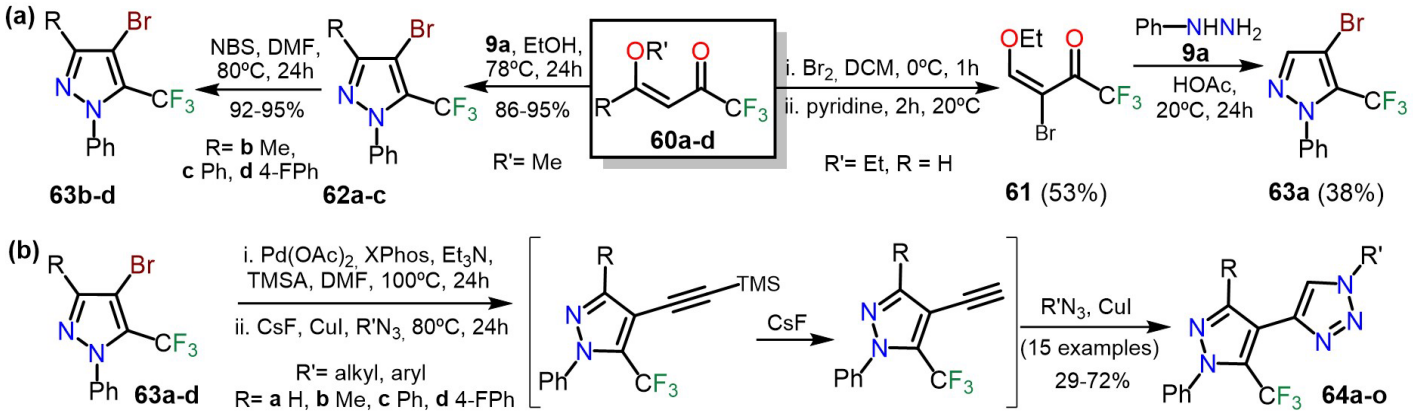
In 2019, Onodera et al. [24] reported a regioselective halogenation of 3-trimethylsilylpyrazole **53** (Scheme 10a). The introduction of halogen atoms at positions 3, 4, and 5 was possible thanks to the different character and orthogonal

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 [25], 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 10b).



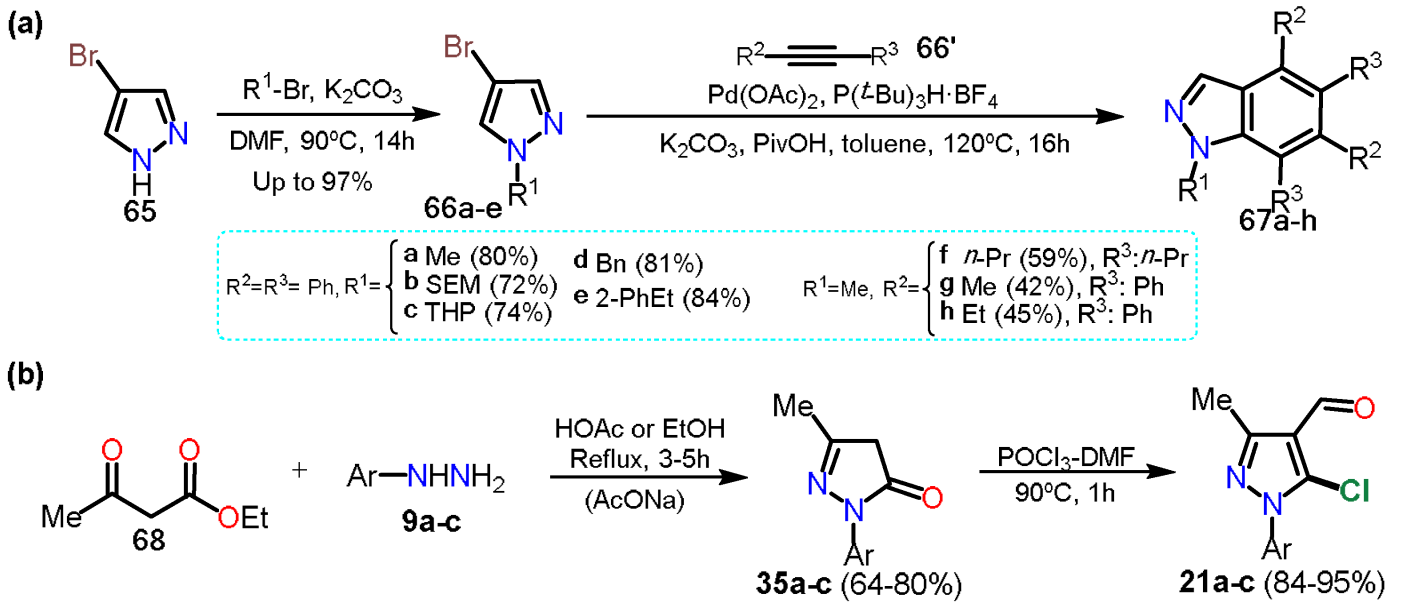
Scheme 10. (**a**) Halogenation of the pyrazole **53** and (**b**) synthesis of the 4-iodopyrazole **59**.

In 2017, Bonacorso et al. [26] 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 11a). 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 11b).



Scheme 11. Synthesis of (**a**) 4-bromo-5-(trifluoromethyl)pyrazoles and their (**b**) synthetical utility.

As it could be seen, 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 [27] 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 12a).



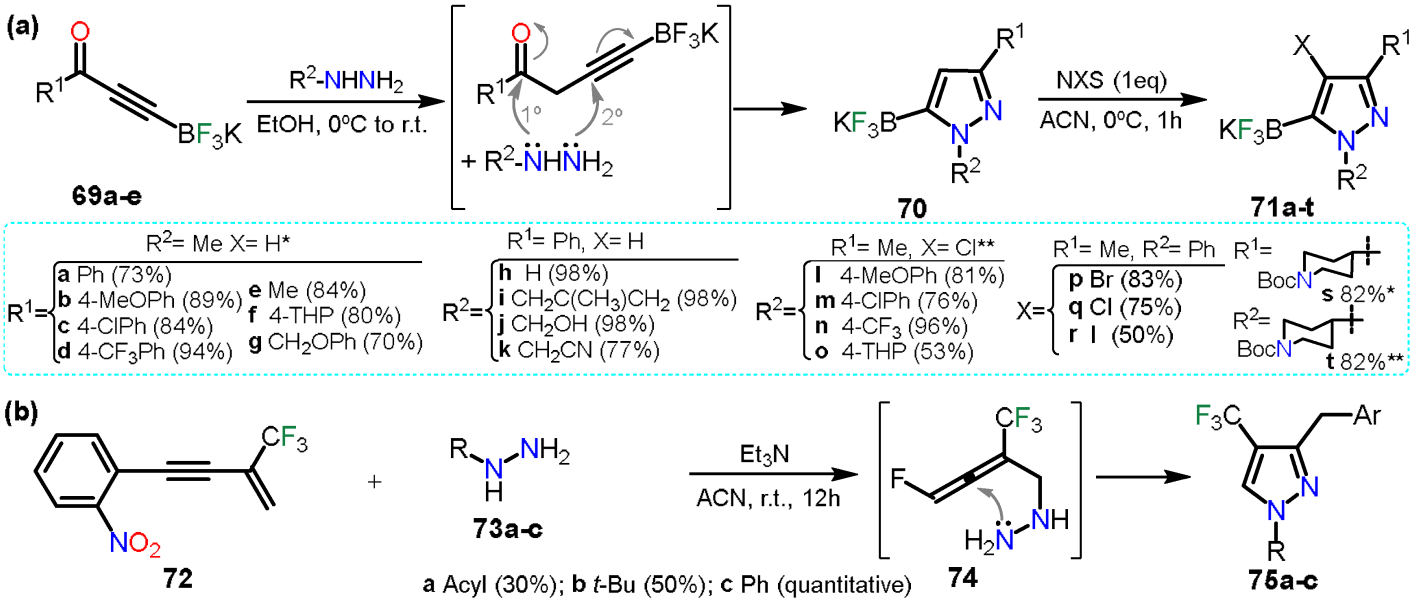
Scheme 12. Synthesis of (**a**) indazoles from 4-bromopyrazoles and of (**b**) 5-chloropyrazoles.

In the above sections, the previous work of Orrego-Hernandez et al. [10] was cited, 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 Scheme 5b and Scheme 8a). Consequently, this methodology is another fundamental example of access to halopyrazoles, particularly 5-chloropyrazoles, from ethyl acetoacetate (**68**) as the starting material (Scheme 12b).

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. [28] reported the regioselective condensation between ynone-trifluoroborates **69a–e** and hydrazine derivatives to obtain pyrazole 5-trifluoroborates **70** (Scheme 13a). The reaction generates a nitrile intermediate just such as the ones studied. Herein, 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.

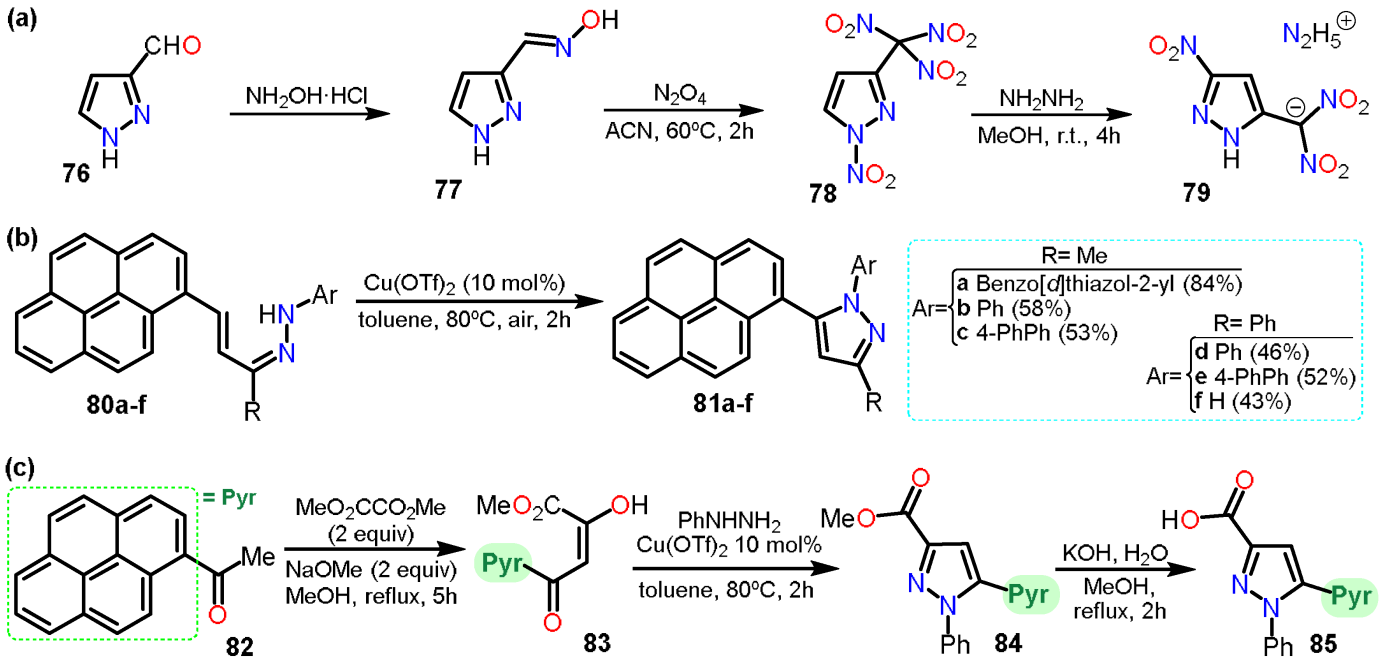


Scheme 13. Synthesis of pyrazoles from (**a**) ynone trifluoroborates and (**b**) from 1,3-enynes.

On the other hand, Wei and co-workers [29] 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 13b). 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**.

Another example is the preparation of nitro-substituted pyrazoles. Zhang et al. [30] synthesized 1-nitro-3-trinitromethylpyrazole (**78**) from 3-formylpyrazole (**76**) (Scheme 14a). 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**. Herein, 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.

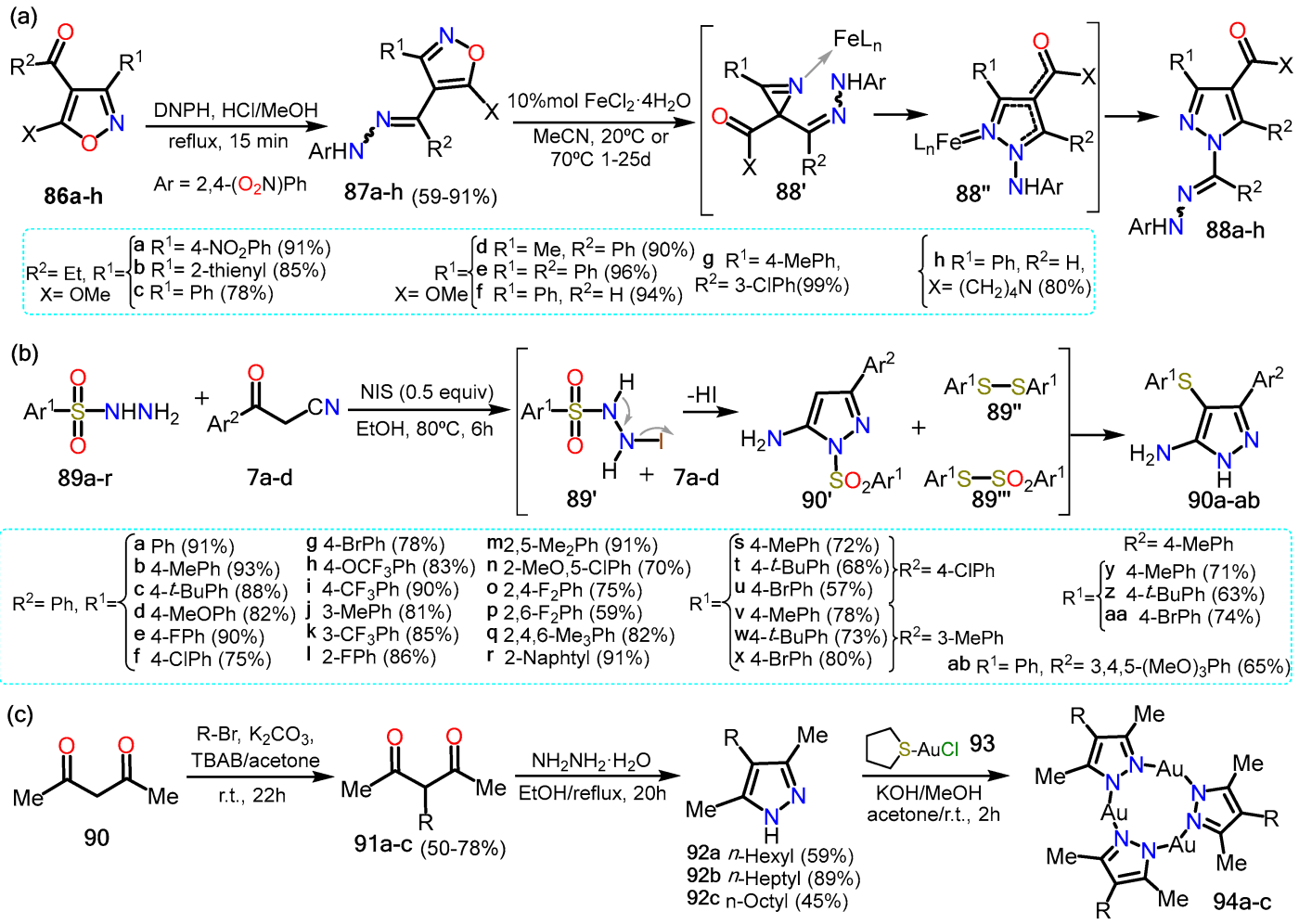


Scheme 14. (**a**) Synthesis of nitro pyrazoles and of pyrene-pyrazoles (**b**) **81** and (**c**) **85**.

Continuing, Sar et al. [31] reported the synthesis of seven pyrene-pyrazole pharmacophores for targeting microtubules (Scheme 14b,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, it is mentioned since they are highly functionalized compounds. In this context, Galenko et al. [32] synthesized 1-aminopyrazole-4-carboxylic acids using an iron II

catalyst (Scheme 15a). 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 15. Synthesis of (**a**) pyrazoles **88**, (**b**) aminopyrazoles **90** and (**c**) trinuclear complexes **94**.

Later, Wei et al. [33] 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 15b). 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. [34] reported phosphorescent trinuclear Au(I) complexes using *NH*-pyrazoles as ligands (Scheme 15c). 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.

References

1. Tsutsumi, O.; Tamaru, M.; Nakasato, H.; Shimai, S.; Panthai, S.; Kuroda, Y.; Yamaguchi, K.; Fujisawa, K.; Hisano, K. Highly efficient aggregation-induced room-temperature phosphorescence with extremely large Stokes shift emitted from trinuclear gold(I) complex crystals. Molecules 2019, 24, 4606.
2. Abu Elmaati, T.M.; El-Taweel, F.M. New Trends in the Chemistry of 5-Aminopyrazoles. J. Heterocycl. Chem. 2004, 41, 109–134.
3. Kallman, N.J.; Cole, K.P.; Koenig, T.M.; Buser, J.Y.; McFarland, A.D.; McNulty, L.A.M.; Mitchell, D. Synthesis of Aminopyrazoles from Isoxazoles: Comparison of Preparative Methods by in situ NMR Analysis. Synthesis 2016, 48, 3537–3543.
4. Hassan, A.S.; Moustafa, G.O.; Awad, H.M.; Nossier, E.S.; Mady, M.F. Design, synthesis, anticancer evaluation, enzymatic assays, and a molecular modeling study of novel pyrazole-indole hybrids. ACS Omega 2021, 6, 12361–12374.
5. Pilakowski, J.; Baumann, G.; Shih, Y.H.; Meckel, T.; Schmidt, B. Design, synthesis and biological evaluation of novel aminopyrazole- and 7-azaindole-based Nek1 inhibitors and their effects on zebrafish kidney development. Bioorg. Med. Chem. Lett. 2021, 53, 128418.
6. Annes, S.B.; Saritha, R.; Chandru, K.; Mandali, P.K.; Ramesh, S. Metal- A nd Solvent-Free Cascade Reaction for the Synthesis of Amino Pyrazole Thioether Derivatives. J. Org. Chem. 2021, 86, 16473–16484.

7. Ren, Z.L.; Liu, H.; Jiao, D.; Hu, H.T.; Wang, W.; Gong, J.X.; Wang, A.L.; Cao, H.Q.; Lv, X.H. Design, synthesis, and antifungal activity of novel cinnamon–pyrazole carboxamide derivatives. Drug Dev. Res. 2018, 79, 307–312.
8. Elnagdy, H.M.F.; Sarma, D. FeCl3/PVP as Green Homogeneous Catalyst to Synthesize 5-Amino-1H-Pyrazole-4-Carbonitriles from Malononitrile Derivatives. ChemistrySelect 2019, 4, 783–787.
9. Sapkal, A.; Kamble, S. Sodium toluene-4-sulfonate as a reusable and ecofriendly catalyst for greener synthesis of 5-aminopyrazole-4-carbonitrile in aqueous medium. J. Heterocycl. Chem. 2020, 57, 3597–3604.
10. Orrego-Hernández, J.; Cobo, J.; Portilla, J. Chemoselective Synthesis of 5-Alkylamino-1H-pyrazole-4-carbaldehydes by Cesium- and Copper-Mediated Amination. Eur. J. Org. Chem. 2015, 2015, 5064–5069.
11. Orrego-Hernández, J.; Portilla, J. Synthesis of Dicyanovinyl-Substituted 1-(2-Pyridyl)pyrazoles: Design of a Fluorescent Chemosensor for Selective Recognition of Cyanide. J. Org. Chem. 2017, 82, 13376–13385.
12. Garzón, L.-M.; Portilla, J. Synthesis of Novel D-π-A Dyes for Colorimetric Cyanide Sensing Based on Hemicyanine-Functionalized N -(2-Pyridyl)pyrazoles: Synthesis of Novel D-π-A Dyes for Colorimetric Cyanide Sensing Based on Hemicyanine-Functionalized N -(2-Pyridyl)pyra. Eur. J. Org. Chem. 2019, 2019, 7079–7088.
13. Orrego-Hernández, J.; Cobo, J.; Portilla, J. Synthesis, Photophysical Properties, and Metal-Ion Recognition Studies of Fluoroionophores Based on 1-(2-Pyridyl)-4-Styrylpyrazoles. ACS Omega 2019, 4, 16689–16700.
14. Ríos, M.-C.; Bravo, N.-F.; Sánchez, C.-C.; Portilla, J. Chemosensors based on N-heterocyclic dyes: Advances in sensing highly toxic ions such as CN− and Hg2+. RSC Adv. 2021, 11, 34206–34234.
15. Kaur, R.; Palta, K.; Kumar, M. Hybrids of Isatin-Pyrazole as Potential α-Glucosidase Inhibitors: Synthesis, Biological Evaluations and Molecular Docking Studies. ChemistrySelect 2019, 4, 13219–13227.
16. Kumar, G.; Siva Krishna, V.; Sriram, D.; Jachak, S.M. Pyrazole–coumarin and pyrazole–quinoline chalcones as potential antitubercular agents. Arch. Pharm. 2020, 353, 2000077.
17. Kumari, P.; Sood, S.; Kumar, A.; Singh, K. Microwave-assisted Vilsmeier-Haack synthesis of Pyrazole-4-carbaldehydes. J. Heterocycl. Chem. 2020, 57, 796–804.
18. Sharma, S.; Singh, V. Exploration of pyrazole based ALDO-X bifunctional building blocks for the synthesis of pyrazole annulated molecular architectures. J. Heterocycl. Chem. 2020, 57, 3735–3762.

19. Nag, S.; Singh, V.; Batra, S. Studies on the Baylis-Hillman reaction of pyrazolecarbaldehydes under the influence of DABCO: Positional effect on the reactivity of the formyl group. Arkivoc 2007, 2007, 185–203.
20. Poletto, J.; da Silva, M.J.V.; Pianoski, K.E.; Willig, J.C.M.; Rosa, F.A. Regiodivergent Synthesis of 3,4- and 4,5-Disubstituted N -Methylpyrazoles from 4-Acyl-1 H -pyrrole-2,3-dione and Methylhydrazine. J. Org. Chem. 2022, 87, 8544–8550.
21. Qiu, F.; Cao, Y.; Zeng, L.; Zhang, C.; Fu, L.; Zhang, J.; Zhu, H.; Shao, J. (2 + 1 + 1 + 1)-Annulation Reactions of Aryldiazonium Tetrafluoroborates with Sulfur Ylides to Polysubstituted Pyrazoles. J. Org. Chem. 2021, 86, 8997–9006.
22. He, B.; Dong, J.; Lin, H.Y.; Wang, M.Y.; Li, X.K.; Zheng, B.F.; Chen, Q.; Hao, G.F.; Yang, W.C.; Yang, G.F. Pyrazole-isoindoline-1,3-dione hybrid: A promising scaffold for 4-hydroxyphenylpyruvate dioxygenase inhibitors. J. Agric. Food Chem. 2019, 67, 10844–10852.
23. Loro, C.; Molteni, L.; Papis, M.; Lo Presti, L.; Foschi, F.; Beccalli, E.M.; Broggini, G. Non-Decarboxylative Ruthenium-Catalyzed Rearrangement of 4-Alkylidene-isoxazol-5-ones to Pyrazole- and Isoxazole-4-carboxylic Acids. Org. Lett. 2022, 24, 3092–3096.
24. Onodera, S.; Kochi, T.; Kakiuchi, F. Synthesis of N-Arylpyrazoles by Palladium-Catalyzed Coupling of Aryl Triflates with Pyrazole Derivatives. J. Org. Chem. 2019, 84, 6508–6515.
25. Zarate, C.; Ardolino, M.; Morriello, G.J.; Logan, K.M.; Kaplan, W.P.; Torres, L.; Li, D.; Chen, M.; Li, H.; Su, J.; et al. Development of Scalable Routes to 1-Bicyclopentylpyrazoles. Org. Process Res. Dev. 2021, 25, 642–647.
26. Bonacorso, H.G.; Dal Forno, G.M.; Wiethan, C.; Ketzer, A.; Zanatta, N.; Frizzo, C.P.; Martins, M.A.P.; Stradiotto, M. Sequential one-pot three-step synthesis of polysubstituted 4-(5-(trifluoromethyl)-1: H -pyrazol-4-yl)-1H-1,2,3-triazole systems. RSC Adv. 2017, 7, 43957–43964.
27. Kim, O.S.; Jang, J.H.; Kim, H.T.; Han, S.J.; Tsui, G.C.; Joo, J.M. Synthesis of Fluorescent Indazoles by Palladium-Catalyzed Benzannulation of Pyrazoles with Alkynes. Org. Lett. 2017, 19, 1450–1453.
28. Fricero, P.; Bialy, L.; Brown, A.W.; Czechtizky, W.; Méndez, M.; Harrity, J.P.A. Synthesis and Modular Reactivity of Pyrazole 5-Trifluoroborates: Intermediates for the Preparation of Fully Functionalized Pyrazoles. J. Org. Chem. 2017, 82, 1688–1696.
29. Wei, L.; Ding, S.; Liu, M.; Yu, Z.; Xiao, Y. Synthesis of Trifluoromethylated Pyrazolidines, Pyrazolines and Pyrazoles via Divergent Reaction of β-CF3-1,3-Enynes with Hydrazines. Org. Lett. 2021, 23, 7718–7723.
30. Zhang, Y.; Li, Y.; Yu, T.; Liu, Y.; Chen, S.; Ge, Z.; Sun, C.; Pang, S. Synthesis and Properties of Energetic Hydrazinium 5-Nitro-3-dinitromethyl-2H-pyrazole by Unexpected Isomerization of N-Nitropyrazole. ACS Omega 2019, 4, 19011–19017.

31. Sar, D.; Srivastava, I.; Misra, S.K.; Ostadhossein, F.; Fathi, P.; Pan, D. Copper-Catalyzed Syntheses of Pyrene-Pyrazole Pharmacophores and Structure Activity Studies for Tubulin Polymerization. ACS Omega 2018, 3, 6378–6387.
32. Galenko, E.E.; Ivanov, V.K.; Novikov, M.S.; Zolotarev, A.A.; Khlebnikov, A.F. Synthesis of N-aminopyrazoles by Fe(II)-catalyzed rearrangement of 4-hydrazonomethyl-substituted isoxazoles. Tetrahedron 2018, 74, 6288–6298.
33. Wei, Y.; Liu, P.; Liu, Y.; He, J.; Li, X.; Li, S.; Zhao, J. NIS-promoted three-component reaction of 3-oxo-3-arylpropanenitriles with arylsulfonyl hydrazides. Org. Biomol. Chem. 2021, 19, 3932–3939.