

RECENT ADVANCES IN THE SYNTHESIS OF NEW PYRAZOLE DERIVATIVES

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Abstract. Pyrazoles have attracted great attention in organic and medicinal chemistry, due to their proven utility as synthetic intermediates for the preparation of diverse bioactive compounds, of coordination complexes, as well as in the design of functional materials. Consequently, the synthesis of functionalized pyrazoles is an important focus of research for synthetic organic chemists. Likewise, fused pyrazoles such as pyrazolo[1,5-*a*]pyrimidines and pyrazolo[3,4-*b*]pyridines have been widely studied due to their varied biological and physicochemical applications based on the important electronic properties of these *N*-heterocycles. Therefore, the preparation of these fused heterocycles and of their functionalized derivatives is of notable interest to both uncover novel derivatives and explore new applications. Several methods have been described in the literature for the synthesis of pyrazoles and of their fused systems in recent years, which mainly involve classical cyclocondensation reactions, some of these are presented in this contribution.

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1. Introduction

Pyrazole is a heteroaromatic compound of 5-membered containing two adjacent nitrogen atoms. *NH*-Pyrazoles can act both as weak bases and moderately weak acids because they have a pyridine-type proton-acceptor nitrogen atom (C=N) and one pyrrole-type nitrogen atom (N-H) with a proton-donor behavior. Likewise, hydrogen bonding interactions and tautomeric properties of these compounds are strictly related to the nature of their heteroatoms as well as by the electronic effect of the substituent groups on the pyrazole core (Figure 1, left).¹ Pyrazole discovery is linked to experiments carried out by the German chemist Ludwig Knorr in 1883, who attempted to synthesize quinoline derivatives with antipyretic activity, but accidentally obtained a pyrazole derivative that he called Antipyrine. Knorr introduced the name pyrazole to this heterocyclic core to denote that was derived from pyrrole by the replacement of a carbon by nitrogen; too, was the first to discover antipyretic action of pyrazole derivatives in man, which has stimulated the interest in pyrazoles chemistry.² Then again, in 1846 Kosuge and Okeda isolated 3-*n*-nonylpyrazole from *Houttuynia cordata* (a plant of the piperaceae family from tropical Asia which showed antimicrobial activity), as well as levo-β-(1-pyrazolyl) alanine from watermelon seeds (*Citrullus vulgaris*). Until these discoveries it was thought that pyrazoles could not be obtained naturally (Figure 1).² The versatility of pyrazole derivatives in synthetic and/or biological applications has been well documented, being even one of the most studied compounds among the azole family, although examples of natural products containing pyrazole moiety are very scarce.^{1,2}

Like the substituted pyrazoles, fused pyrazoles are an important class of *N*-heterocycles due to the wide spectrum of applications that exist in a vast number of their derivatives.¹⁻³ Likewise, natural products

bearing a condensed pyrazole structure are also rare, but it is important to mention the pyrazolo[4,3-*d*]pyrimidine of natural origin Formicin A, which is a C-nucleoside that exhibits antitumor and antiviral properties.^{3a} In general, biological and pharmacological activities of these compounds containing pyrazole nucleus fused with five- and six-membered heterocycles have been extensively described.^{3a-f} In particular, pyrazolo[1,5-*a*]pyrimidines and pyrazolo[3,4-*b*]pyrimidines have interest in drug discovery for its analogy to purines, and nowadays have gained more importance due to their broad range of application in medicinal chemistry,^{3b-d} as well as in material sciences because of their interesting photophysical properties.^{3e,f} For example, the anxiolytic agents Ocinaflon^{3c} and Tracazolate^{3d} have these structural motif (Figure 2).

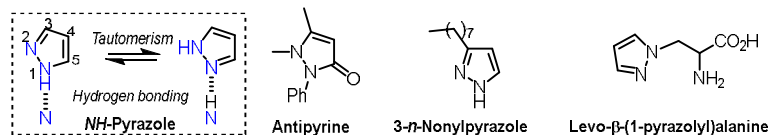


Figure 1. Pyrazole derivatives of synthetic and natural importance.

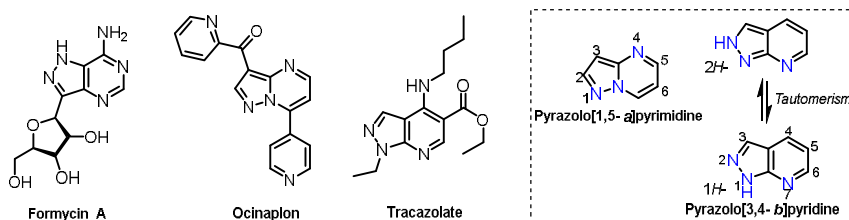


Figure 2. Examples of pyrazolo[1,5-*a*]pyrimidines and pyrazolo[3,4-*b*]pyridines.

The importance of pyrazoles, as well as of their previously mentioned fused systems had led to the development of various methods for the respective syntheses, and most of them have been compiled in several comprehensive reviews.¹⁻³ These methods mainly involve classical cyclocondensation reactions between 1,3-*bis*-electrophilic reagents with compounds having the hydrazine moiety to obtain pyrazoles,^{1,2,5} or with 5-aminopyrazoles to form fused pyrazoles.^{3b-f} Alternatively, the [3+2]-cycloaddition reactions of 1,3-dipoles (diazole derivatives) with alkynes have also been used for the efficient pyrazole ring construction.¹

Therefore, this contribution constitutes an important complement to the state about synthetic methods relating some pyrazole derivatives such as aminopyrazoles and formylpyrazoles, as well as the fused systems pyrazolo[1,5-*a*]pyrimidines and pyrazolo[3,4-*b*]pyridines (Figure 2, right), but special emphasis is given on highly functionalized derivatives.

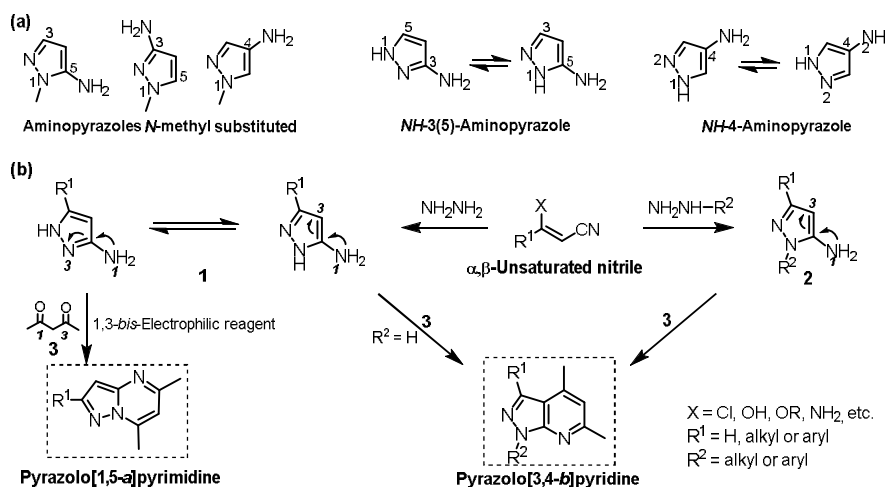
2. Functionalized pyrazoles

The wide range of biological and synthetic applications presented by pyrazoles has made them crucial goals to various organic and medicinal chemistry research groups.^{1,2} Notably, various pyrazole derivatives have been used to achieve the formation of metal complexes due to the presence of the pyridine-like N-atom in the respective ligand.¹ In addition, pyrazoles are π -excess compound that can react easily with electrophilic reagents at position 4 and thus are very poorly reactive towards nucleophiles, which preferentially attacks at positions 3 and 5.^{1,2} Indeed, examples of nucleophilic substitution reactions on pyrazoles are scarce; however, suitably substituted pyrazoles can increase their reactivity to both electrophiles and nucleophiles, *i.e.* with the introduction of electron-donating (EDG) or electron-withdrawing (EWG) groups, respectively.^{1,2} For example, aminopyrazoles have been widely used as highly reactive precursors for preparation of fused pyrazoles by their interaction with 1,3-*bis*-electrophiles.⁴ Therefore, the physicochemical properties of pyrazoles depend mainly on the nature of their nitrogen atoms and the electronic effect of the substituent groups on the ring, which displays the great importance of the functionalized pyrazoles. Numerous methods have been developed for obtain substituted pyrazoles, which

involve mainly reactions between 1,3-*bis*-electrophilic reagents with hydrazine derivatives, and a few others include 1,3-dipolar cycloadditions of diazo compounds with alkynes.^{1,2} Pyrazole ring allows for structural changes at positions 1, and 3-5 during ring-construction and/or subsequent functionalization steps.^{1,2} In the present contribution more emphasis is given for the synthetic strategies developed for the synthesis of functionalized pyrazoles with amino and formyl groups *via* cyclocondensation reactions from hydrazine derivatives. Thus, generalities and synthetic information about aminopyrazoles and formylpyrazoles as well as the synthetic utility of some representative pyrazoles are described below.

2.1. Aminopyrazoles

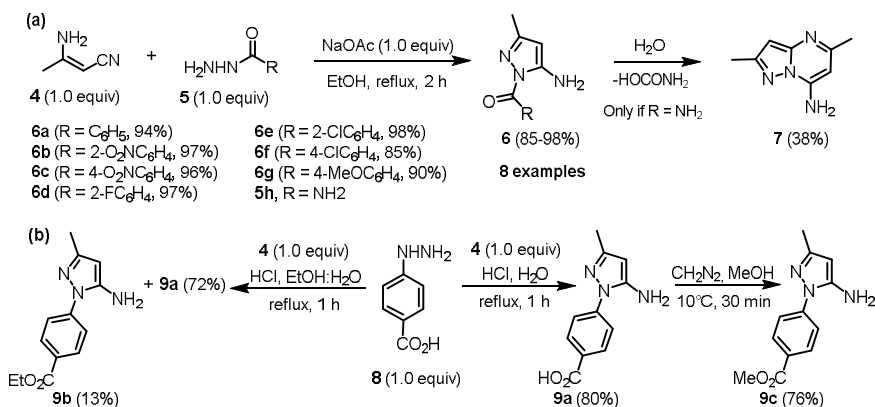
Aminopyrazoles are π -excess highly reactive compounds toward diverse electrophiles. There are three types of *N*-substituted aminopyrazoles (*i.e.* 3-, 4-, and 5-amino) and only two types of *NH*-derivatives (*i.e.* 3- and 4-amino) by ring tautomerism (Scheme 1a). Among these monoamines, *NH*-3-aminopyrazoles **1** and *N*-substituted 5-aminopyrazoles **2** are the derivatives most investigated in heterocyclic chemistry, which are obtained by cyclocondensation between α,β -unsaturated nitriles (containing at *C* β an easily displaceable) and hydrazine or *N*-substituted hydrazines, respectively (Scheme 1b).⁵⁻⁷ It is important to note that amines **1** and **2** have been extensively studied as 1,3-*bis*-nucleophilic reactants in cyclocondensation reactions with various 1,3-*bis*-electrophiles to obtain pyrazolo[1,5-*a*]pyrimidines and pyrazolo[3,4-*b*]pyridines, respectively. General examples of the preparation of these fused systems using acetylacetone **3** as starting reagent are shown in Scheme 1b.^{3b-f} Synthetic information and some applications about these fused *N*-heterocycles are described in later sections, while overviews and synthetic details about aminopyrazoles are discussed below.



Scheme 1. (a) Examples of aminopyrazoles, (b) synthesis and their use as 1,3-*bis*-nucleophiles.

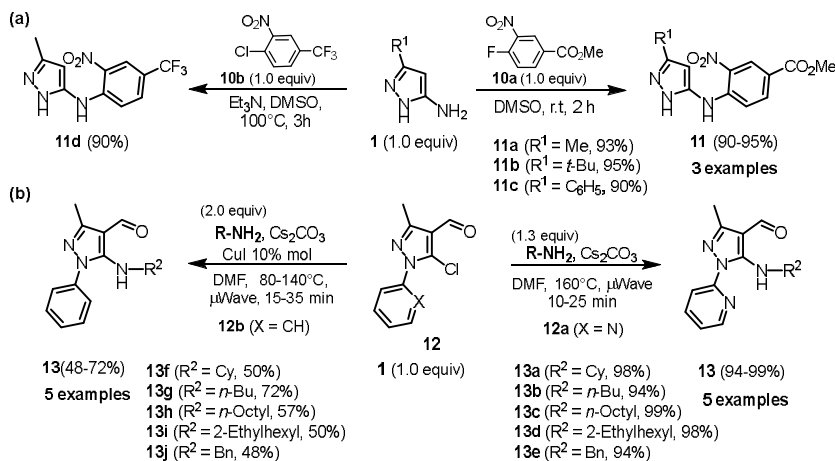
A decade ago, Quiroga, Portilla, and co-workers reported an efficient and direct synthesis of 5-amino-1-arylpyrazoles **6** *via* the reaction of β -aminocrotonitrile **4** with the respective hydrazide **5** by refluxing ethanol in presence of sodium acetate. The synthesis was carried out in high yields but the reaction produced the unexpected 7-aminopyrazolo[1,5-*a*]pyrimidine **7** when semicarbazide **5h** was used, since the pyrazole preformed **6h** probably suffer hydrolysis and later cyclocondensation with a second molecule of **4** (Scheme 2a). This synthetic approach was distinguished by their operational simplicity *vs.* other methods, because for example, the acylation of *NH*-3-aminopyrazoles gives a mixture of products.⁶ Likewise, Portilla *et. al.* reported a supramolecular study based on single-crystal X-ray diffraction of three 4-(5-aminopyrazol-1-yl)benzoates **9** in good yields, which were obtained starting from **4** and the arylhydrazine **8** in presence of concentrated hydrochloric acid (Scheme 2b). When the reaction was carried out using reflux in ethanol:water (\pm 1:2 v/v), the expected amino acid **9a** (major product) was obtained mixed with the amino ester **9b** (minor product), while the pyrazole **9a** was obtained as single-product under reflux

in only water. Chemoselective esterification of **9a** with diazomethane offered the respective methyl ester **9c** in good yield, which could be important to facilitate its manipulation as 5-aminopyrazolic reagent in later reactions.⁷ The preparation of the benzoic acid **9a** was inspired by the fact that this compound could be used as a precursor in novel solid-phase synthesis protocols based on the chemistry of 5-aminopyrazoles *via* its coupling with the Wang resin.^{8b}



Scheme 2. Synthesis of *N*-aryl-5-aminopyrazoles (a) **6** and (b) **9** from β -aminocrotonitrile (**4**).

Therefore, Portilla *et al.* proposed to obtain novel *N*-substituted 5-aminopyrazoles by the expected attack of the more nucleophilic nitrogen of the pyrazolic ring (NH group) of **1** over the activated halide **10**. However, the unexpected nucleophilic aromatic displacement over **10** by the NH₂ group of **1** leading to *NH*-3-(*N*-arylamino)pyrazoles **11** in excellent yields. Possibly, the steric effect of the nitro group on the aryl halide **10** is an important factor in determining the course of reactions (Scheme 3a).⁸

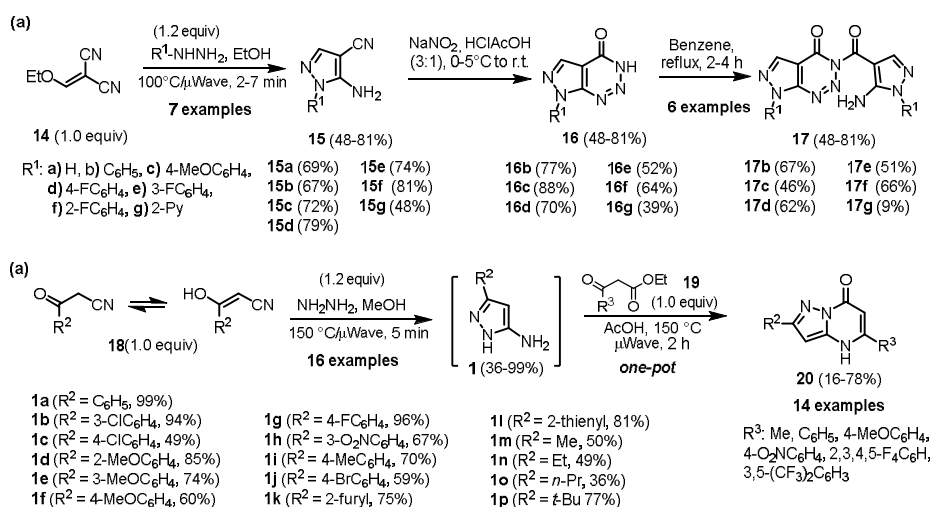


Scheme 3. Synthesis of (a) *NH*-3-arylamino pyrazoles **11** and (b) 5-alkylamino-1-arylpazoles **13**.

More recently, Portilla and co-workers carried out the synthesis of 5-alkylamino-*N*-arylpazoles **13** by a microwave-assisted and Cs-mediate nucleophilic attack of the appropriate primary alkylamine over the poorly activated 5-chloropyrazoles **12**.⁹ Despite the little reactivity of pyrazoles towards the nucleophilic attack,^{1,2} the synthesis of **13** was carried out in short reaction times and in moderate to excellent yields according to the effect of the aryl group at position 1 of the pyrazolic ring. For example, the

electron-withdrawing nature of the 2-pyridyl group in the pyrazole **12a** favors the nucleophilic aromatic substitution reaction, and indeed, a catalytic amount of copper (I) and an excess of alkylamine when using the *N*-phenylpyrazole **12b** should be added to the reaction mixture (Scheme 3b).⁹ Notably, under these optimized reaction conditions the corresponding imine formation was not observed.

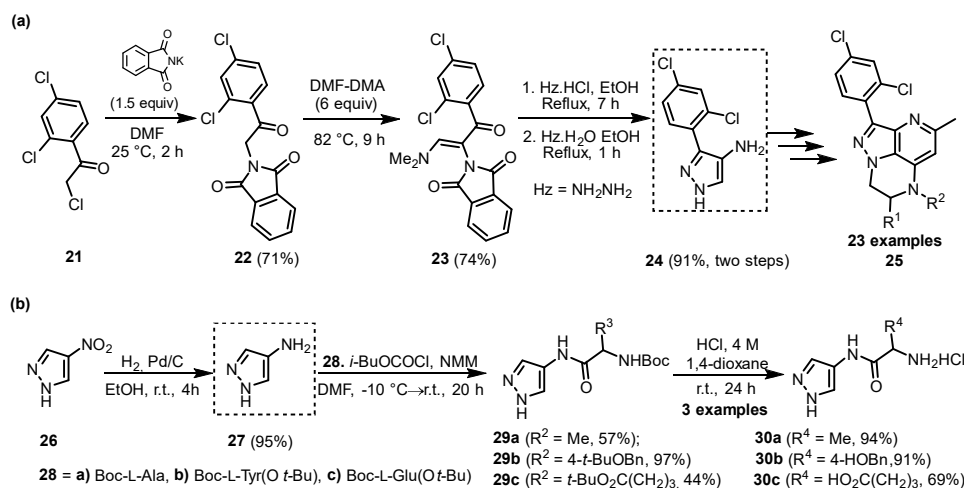
In the above example microwave-assisted organic synthesis (MAOS) was used. This synthetic approach has proven to be efficient and environmentally benign due to its simplicity in operation, short reaction times, and clean products formation leading to better yields, selectivities, and easier workup. In addition, MAOS has been very useful in achieving various *N*-heterocycles of synthetic, biological, and photophysical interest;¹⁰ thus, in all sections of this contribution its use is mentioned, considering also that many of our works on pyrazoles have been carried out *via* microwave-assisted reactions. In this way, in 2018 Colomer *et al.* obtained 5-aminopyrazoles **15** in good yields *via* the reaction under microwave of ethoxymethylenemalonitrile **14** with the respective hydrazine at 100 °C (2-7 min) in ethanol. Pyrazoles **15** were subjected to diazotization conditions to prepare pyrazolo[3,4-*d*][1,2,3]triazinones **16**, which by thermal treatment in benzene at reflux (2-4 h) afforded 3-(5-aminopyrazol-4-ylcarbonyl)pyrazolotriazinones **17** (Scheme 4a). These results evidence the synthetic utility of 5-aminopyrazoles as precursors of novel pyrazolo-fused heterocycles.¹¹ Likewise, Stephens and co-workers reported a one-pot microwave-assisted synthesis of pyrazolo[1,5-*a*]pyrimidinones **20** as well as an efficient and general synthesis also under microwave of a *NH*-3-aminopyrazoles library **1**. Amines **1** were obtained from β -keto nitriles **18** in moderate to excellent yields at 150 °C for 5 minutes in methanol, but authors then focused their attention on carrying out cyclocondensation reactions with β -ketoesters **19** in the same reactor without further isolation of **1** due to its goof formation and reactivity (Scheme 4b).¹²



Scheme 4. Microwave-assisted synthesis of (a) 5-aminopyrazoles **15** and (b) *NH*-3-aminopyrazoles **1**.

Oppositely, 4-aminopyrazoles are less popular *vs.* 3- or 5-aminopyrazoles, and indeed, most of the existing reports are patents. These amines are obtained mainly by nitration and subsequent reduction of the appropriate and, in general, commercially available pyrazole, *i.e.*, without substitution at position 4.¹³⁻¹⁸ 4-Aminopyrazoles synthesis has been carried out successfully both from *NH*-pyrazoles and *N*-substituted pyrazoles according to the required substitution at the other positions of the ring.¹⁴ An interesting and alternative example concerns the amination-derivatization-cyclization sequence introduced in 2005 by Goss *et al.* for the synthesis of *NH*-4-amino-3-(2,4-dichlorophenyl)pyrazole **24** in three steps and 48% overall yield. Amination of α -chloro-2,4-dichloroacetophenone **21** with potassium phthalamide afforded the protected 2-aminoketone **22**, which reacted *via* a condensation with *N,N*-dimethylformamide dimethylacetal to provide the corresponding β -enaminone **23**. Finally, the cyclocondensation reactions of **23** with hydrazine

provided the product **24** in very good yield (Scheme 5a). Pyrazole **24** was used efficiently for the synthesis of a novel series of tricyclic pyrazolo[4,3-*b*]pyridines **25**, which exhibited activity as corticotropin-releasing antagonists (Factor-1).¹⁵ More recently, Maccallini *et al.* described the synthesis of 4-(acylamino)pyrazoles **30** starting from 4-nitropyrazole **26** in three steps and overall yield up to 84% by a conventional sequence. Catalytic reduction of **26** was performed to obtain *NH*-4-aminopyrazole **27**, which was coupled with the fully protected amino acids **28** in the presence of *i*-BuOCOCl and *N*-methylmorpholine (NMM) to obtain the Boc-protected pyrazoles **29**. This intermediate was deprotected with HCl in dioxane to give products **30** (Scheme 5b), which presented moderate *in vitro* NOS (Nitric Oxide Synthases) inhibitory activity by measuring the conversion of L-arginine to L-citrulline using a validated HPLC method with fluorescence detection.¹⁶

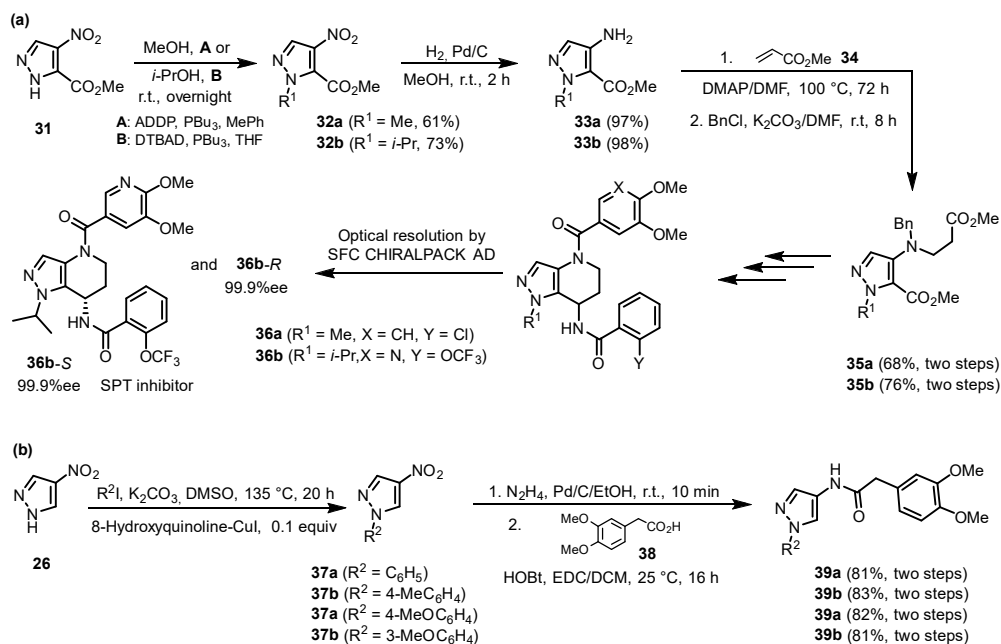


Scheme 5. Synthesis of (a) 4-amino-3-(2,4-dichlorophenyl)pyrazole (**24**) and (b) 4-(acylamino)pyrazoles **29**.

Imamura and co-workers in 2018 developed a synthesis of 4-dialkylaminopyrazoles **35** in four steps from the 4-nitropyrazole **31** and overall yield up to 54%. Mitsunobu reaction of **31** for overnight proceeded in a regioselective manner to give *N*-alkylpyrazoles **32** in good yields, and catalytic reduction of their nitro group afforded 4-aminopyrazoles **33** in quantitative yields. Aza-Michael reaction of **33** with methyl acrylate **34** gave β -(pyrazol-4-ylamino)esters **35**, which were converted to dialkyl derivatives **35** by benzylation reaction (Scheme 6a). These 4-dialkylaminopyrazoles **34** were successfully used for the synthesis of biologically important fused pyrazoles **36a** and **36b** as a racemates. Optical resolution of **36b** was conducted by Chiralpak AD to provide **36b-S** and **36b-R** with $\geq 99.9\%$ ee. Absolute configuration of **36b-S** was determined to be *S* via its X-ray crystallographic analysis. The tetrahydropyrazolo[4,3-*b*]pyridine **36b-S** potently inhibited both serine palmitoyltransferase (SPT) enzyme (IC₅₀=1.2 nM) and HCC4006 cell growth (IP=3.9 nM), and showed good pharmacokinetic properties in mice (F=53%).¹⁷ In this same year, Wang *et al.* carried out the synthesis of novel *N*-aryl-4-acylamino pyrazoles **39** by coupling of 2-(3,4-dimethoxyphenyl)acetic acid (**38**) and the respective aminoderivative obtained from *N*-aryl-4-nitropyrazoles **37**. Initially, the Cu-mediated *N*-arylation of *NH*-4-nitropyrazole (**26**) afforded intermediates **37**, and their catalytic reduction with hydrazine hydrate in ethanol produced the expected amine, which were used without further purification (Scheme 6b). Amides **39** and other pyrazole derivatives were evaluated for their inhibitory effects on BRAF^{V600E} kinase and three cancer cell lines, HT29 (BRAF^{V600E}), A375 (BRAF^{V600E}), WM1361 (BRAF^{WT}). Compounds containing the 4-methoxyphenyl group at position 1 showed the best biological activity.¹⁸

More details about the synthetic utilities of *NH*-3-aminopyrazoles and *N*-substituted 5-aminopyrazoles are described in later sections. Particularly, the use of these 1,3-*bis*-nucleophilic pyrazoles as starting

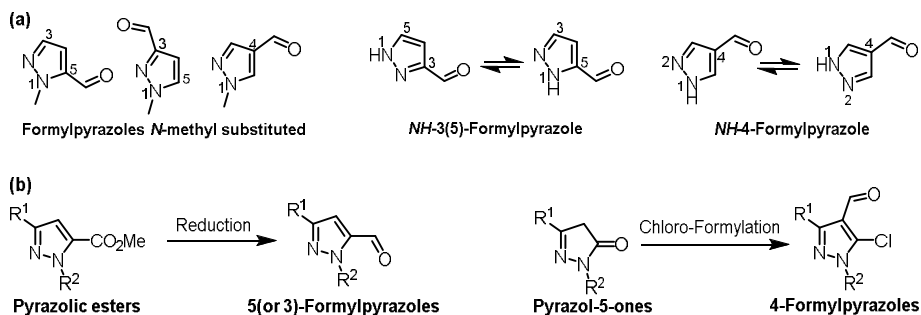
reagents in cyclocondensation reactions with various 1,3-bis-electrophiles to obtain fused pyrazoles is described.



Scheme 6. Synthesis of (a) 4-dialkylaminopyrazoles **35** and (b) *N*-aryl-4-(acylamino)pyrazoles **39**.

2.2. Formylpyrazoles

Formylpyrazoles occupy a noticeable place in the field of organic and medicinal chemistry despite somewhat being less popular than the amino derivatives, since such heteroaryl aldehydes are key intermediates in obtaining a wide range of biologically active compounds.^{1,2,19} There are several types of formylpyrazoles similarly to amines previously described and among these (Scheme 7a), the 3- and 5-formyl derivatives are commonly obtained by reduction reactions of the respective pyrazolic ester,¹⁹ while the 4-formylpyrazoles have been obtained by formylation reactions on the ring due to the high electron density of the carbon atom at position 4 of the pyrazolic ring.^{1,2,20-23}

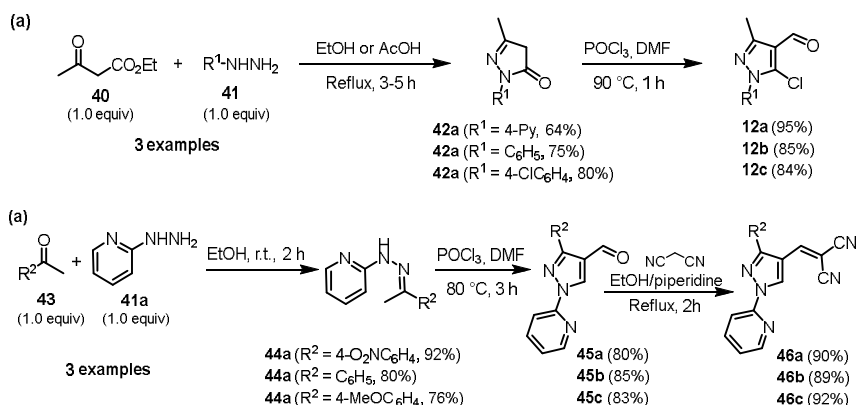


Scheme 7. (a) Types of formylpyrazoles and (b) some of their synthetic approaches.

Consequently, these heteroaryl aldehydes are obtained mainly starting from precursors that already have the pyrazolic ring, *i.e.*, pyrazolic esters, pyrazol-5-ones, unsubstituted pyrazoles, etc. (Scheme 7b). In

contrast to the widely studied 3- and 5-aminopyrazoles, 3- and 5-formyl derivatives are less frequent and most of the existing reports on these aldehydes are pharmaceutical patents, although anyway if there are abundant reports on 4-formylpyrazoles. Synthetic information and some general applications about all formylpyrazole derivatives are discussed below.

In this way, the work reported by Portilla and co-workers about the preparation of 5-alkylamino-4-formylpyrazoles **13** starting from 5-chloro-4-formylpyrazoles **12** is cited again (see Scheme 3b),⁹ since this precursor was obtained in good yields by chloroformylation of the appropriate pyrazolone **40** under Vilsmeier conditions. Pyrazol-5-onas **42** were synthesized *via* the classical cyclocondensation reaction between ethyl acetoacetate (**40**) and the respective arylhydrazine **41** (Scheme 8a).^{9b} Recently, Orrego-Hernández and Portilla synthesized a family of 4-(2,2-dicyanovinyl)pyrazoles **46** in 58-66% overall yield for three reaction step, which allowed us to design and successfully apply an "on-off" fluorescent chemosensor **46c** (4-methoxyphenyl substituted) for the selective recognition of cyanide (CN⁻). Design of the probe **46c** was based on a Michael-type nucleophilic addition reaction of CN⁻ on the C=C bond of the dicyanovinyl derivative *via* an intramolecular charge transfer (ICT) mechanism favored by the electronic nature of its substituent groups. Condensation between acetophenones **43** and 2-hydrazinepyridine **41a** proceeded efficiently to give hydrazones **44**, and their cyclization-formylation of Vilsmeier-Haack afforded 4-formylpyrazoles **45**, which were converted to products **46** by a Knoevenagel reaction in ethanol and piperidine as a catalyst (Scheme 8b).²¹

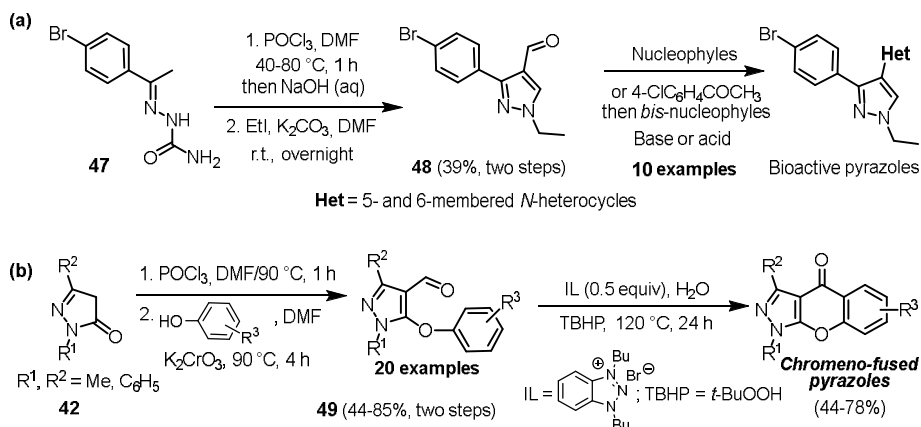


Scheme 8. Synthesis of (a) 5-chloro-4-formylpyrazoles **12** and (b) 4-(2,2-dicyanovinyl)pyrazoles **46**.

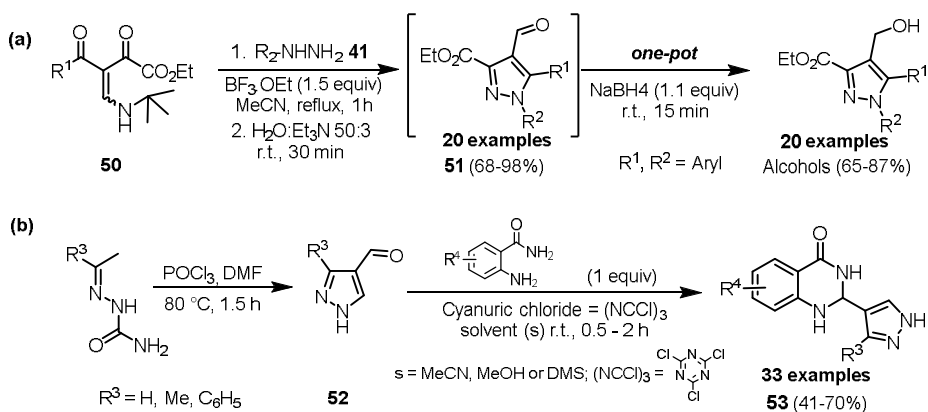
Similarly, Fahmy *et al.* reported the synthesis of 3-(4-bromophenyl)-1-ethyl-4-formylpyrazole **48** as precursor of novel pyrazoles substituted at position 4 with 5- and 6-membered N-heterocycles, which showed anti-cancer activity on various human cancer cell lines (*i.e.* hepatocellular carcinoma HepG2, breast cancer MCF-7, lung carcinoma A549 and prostatic cancer PC3). Heteroaryl aldehyde **48** was obtained starting from the semicarbazone **47** *via* the aforementioned Vilsmeier-Haack reaction, and its interaction with different nucleophiles directly afforded the new products or the corresponding heterocyclic chalcone as an intermediate of these novel bioactive pyrazoles (Scheme 9a).²² On the other hand, Liu and co-workers obtained a combinatorial library of novel chromeno-fused pyrazoles (in 44-78% yield) by a green method that involves intramolecular annulation (oxidative cross-coupling reactions) of 5-(aryloxy)-4-formylpyrazoles **49** using ionic liquid (IL) as promoter, water as solvent, and *tert*-butyl hydroperoxide (TBHP) as oxidant without any metal additives or catalysts. Precursor aldehydes were obtained in two steps from the respective pyrazolone **42** in 44-85% overall yield by Vilsmeier-Haack chloroformylation (Scheme 9b).²³

Following an alternative approach, da Silva *et al.* carried out a regioselective synthesis of 3,5-disubstituted 4-formyl-*N*-arylpyrazoles **51** in 68-95% yield by the cyclocondensation reaction of β -enamino diketones **50** with arylhydrazines **41**. Structural modifications in **50** (presence of an enamino group with high steric demand, *i.e.* *i*-Pr or *t*-Bu) allied to the Lewis acid carbonyl activator BF₃ were

strategically employed for the selectivity control. In addition, authors developed an efficient protocol for the derivatization of 4-formylpyrazoles **53** to the corresponding alcohols from β -enamino diketone substrates and arylhydrazine in a one-pot procedure without further isolation of **51** due to its almost quantitative formation and simple purification process. This synthetic approach was distinguished by their high operational simplicity and ecocompatibility in terms of energy and waste. (Scheme 10a).²⁴ More recently, Zhang *et. al.* obtained a series of 2-(pyrazol-4-yl)-2,3-dihydroquinazolin-4-ones **53** in moderate to good yields (41-70%) from 4-formyl-*NH*-pyrazoles **52**. Some of these novel products **53** exhibited strong inhibitory activity against Transient Receptor Potential Melastatin 2 (TRPM2, a Ca^{2+} -permeable cationic channel) with IC_{50} =3.7 $\mu\text{g/mL}$ for the most active compound, and notably the TRPM8 channel was not affected (Scheme 10b).²⁵



Scheme 9. Obtention of (a) novel 1,3,4-trisubstituted pyrazoles and (b) chromeno-fused pyrazoles.

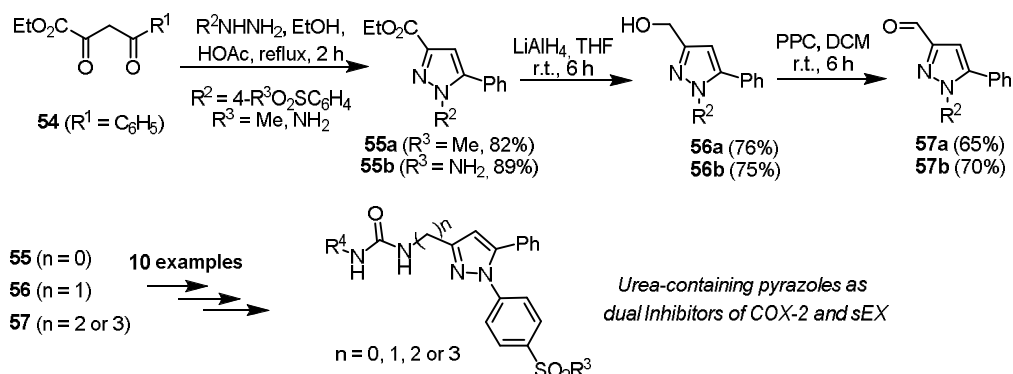


Scheme 10. Synthesis of (a) 4-formyl-*N*-arylpyrazoles **51** and (b) 2-(pyrazol-4-yl)quinazolones **53**.

As already mentioned, 3- and 5-formylpyrazoles are usually obtained by reduction reactions of the respective pyrazolic ester, which in turn is obtained through cyclocondensation reactions between a β -diketoester with the appropriate hydrazine.^{19,26-28} Some examples about preparation and synthetic utility of these heteroaryl aldehydes are shown below (Schemes 11 and 12).

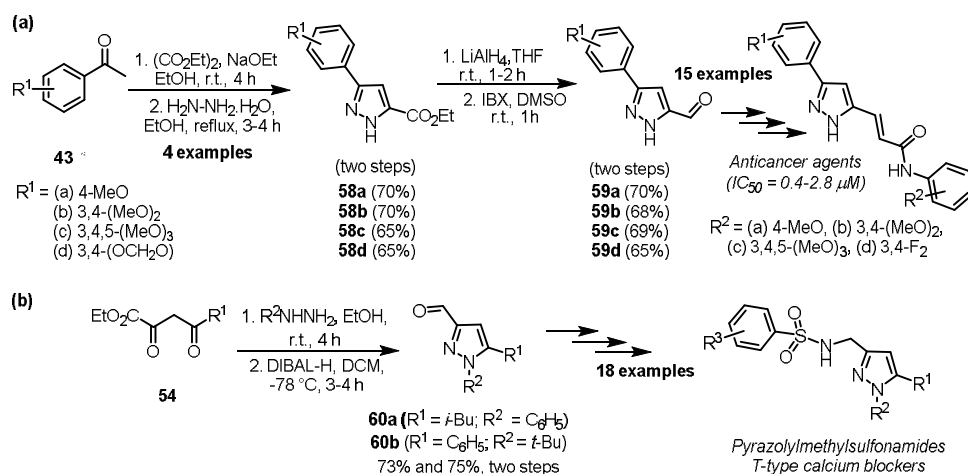
In 2011, Hammock and co-workers reported the use of 3-formylpyrazoles **57** as well as of their precursors (pyrazolic esters **55** and pyrazolic alcohols **56**) as building blocks of new urea-containing pyrazoles. Some of these pyrazoles exhibited dual inhibitory activity on cyclooxygenase-2 (COX-2) and

soluble epoxide hydrolases (sEX), *i.e. in vitro* using recombinant enzyme assays and *in vivo* using a lipopolysaccharide (LPS) induced model of pain in rats. Interestingly, the dual inhibitors exhibited enhanced *in vivo* antiallodynic activity in a nociceptive behavioral assay with a good pharmacokinetic profile.²⁶ Pyrazolic esters **55** intermediates were prepared *via* the regioselective cyclocondensation under reflux in ethanol between ethyl 2,4-dioxo-4-phenylbutanoate (**54**) and the respective sulfonylphenylhydrazine (4-methyl- or 4-amido-). Future, reduction of **55** by lithium aluminum hydride in tetrahydrofuran afforded pyrazolic alcohols **56**, which were oxidized to the respective 3-formylpyrazoles **57** using pyridinium chlorochromate (PCC) in dichloromethane (DCM) at room temperature (Scheme 11).²⁶



Scheme 11. Synthesis of (a) 3-formyl-*N*-arylpyrazoles **57** and their precursors **55** and **56**.

Analogously, Kamal *et al.* carried out the preparation of alkoxyphenyl-substituted 5-formyl-*NH*-pyrazoles **59** as strategic intermediates of (*E*)-3-(pyrazol-5-yl)acrylamides synthesis, which have ability to inhibit the growth of various human cancer cell lines (*i.e.* HeLa, DU-145, A549 and MDA-MB231) and most of them exhibit considerable cytotoxic effects (Scheme 12a).²⁷ The preparation of 5-formylpyrazoles **59** was initiated with the sodium ethoxide-mediated condensation between alkoxy-substituted acetophenones **43** and diethyl oxalate affording the corresponding β -diketoester (analogous to **54**), which by its cyclocondensation with hydrazine hydrate in ethanol produced pyrazole esters **58** in two steps and overall yield up to 70%.



Scheme 12. Synthesis of (a) 4-formyl-*NH*-pyrazoles **59** and (b) *N*-substituted 3-formylpyrazoles **60**.

Subsequent, treatment of **55** with lithium aluminum hydride afforded the expected 5-pyrazolylmethanol **56**, which was oxidized to the respective heteroaryl aldehydes **59** using 2-iodoxybenzoic acid (IBX) in dimethylsulfoxide (Scheme 12a).²⁷

In this same way, Nam and co-workers prepared the *N*-substituted 3-formylpyrazoles **60** but only two reaction steps were used starting from β -diketoester **54** due to a direct conversion of the respective intermediate pyrazolylolester to aldehydes **60** with diisobutylaluminum hydride (DIBAL-H) as a selective reductor agent. Thereby, compounds **60** were obtained in two steps (cyclocondensation and selective reduction) and 63-75% overall yield.²⁸ These aldehydes were successfully used as precursors of a novel series of aryl(1,5-disubstituted pyrazol-3-yl)methyl sulfonamide derivatives, whose design was inspired by the chemical motifs of known antiepileptics possessing T-type calcium inhibitory activity. As expected, some of the tested compounds in the respective bioassays exhibited good T-type channel inhibitory potency with low hERG channel and CYP450 inhibition (Scheme 12b).²⁸

3. Fused pyrazoles

As already mentioned in the introductory section, fused pyrazoles have a wide range of biological activities, which has led to several of their derivatives being applied in pharmaceutical, agricultural, and industrial fields. Therefore, the synthesis and transformations of these condensed heterocycles have been and will continue to be a research topic of considerable interest to a diverse group of researchers who work in organic synthesis, drug discovery and agrochemical agents.^{2,3} Within the vast number of these heterocyclic systems that can be found in the literature, those that containing pyrazole nucleus fused with six-membered *N*-heterocycles, such as pyridine or pyrimidine stand out.²⁻⁴ For instance, pyrazolo[1,5-*a*]pyrimidines and pyrazolo[3,4-*b*]pyrimidines are important derivatives due to their proven utility as bioactive compounds, ligands of metal complexes, and as functional molecules in material science. The numerous both traditional and novel synthetic approaches of these *N*-heterocycles are mainly based on the construction of the six-membered ring as a result of intramolecular heterocyclization starting from the pyrazole appropriate.^{3b-f,4} Overviews and synthetic details about pyrazolo[1,5-*a*]pyrimidines and pyrazolo[3,4-*b*]pyrimidines are described below as well as the synthetic utilities of some fused pyrazoles.

3.1. Pyrazolo[1,5-*a*]pyrimidines

From historic point of view, pyrazolopyrimidines were first described as adenosine receptor antagonists,²⁹ with pyrazolo[1,5-*a*]pyrimidine derivatives being the most investigated in medicinal chemistry. This fused heterocyclic core is a rigid planar system, which allows for structural modifications at positions 2, 3, 5, 6, and 7 during ring-construction and subsequent functionalization steps. The first comprehensive review on this attractive heterocyclic core appeared only in 2004,³⁰ and other reviews on medical applications and synthetic approaches to its access have appeared more recently.³¹⁻³³ The continual interest in the chemistry of pyrazolo[1,5-*a*]pyrimidines is mainly due to its ubiquity in numerous biologically and pharmacologically active compounds. In addition, versatile reactivity of these *N*-heterocycles makes them very useful building block in medicinal chemistry and drug design. Some commercially available drugs containing pyrazolo[1,5-*a*]pyrimidine scaffold such as Zaleplon, Indiplon, Dinaciclib, Ocinaflon, and Anagliptin are shown in Figure 3 with their approved activities.³³

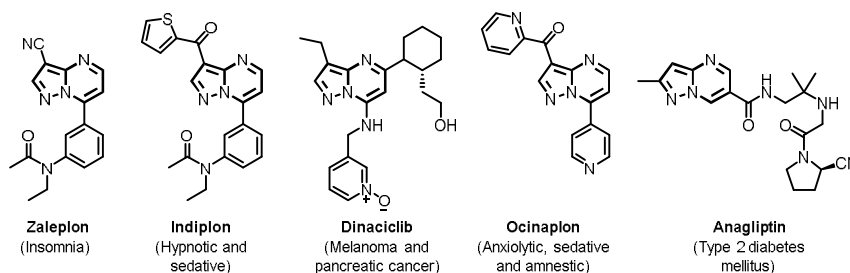
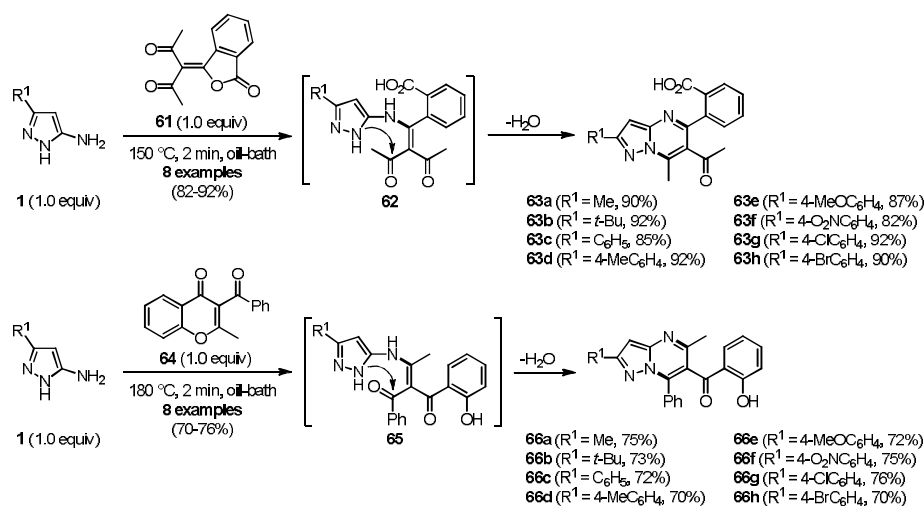


Figure 3. Drugs containing pyrazolo[1,5-*a*]pyrimidine scaffold.

Due to their wide spectrum of pharmacological properties, the synthesis and functionalization of pyrazolo[1,5-*a*]pyrimidine nucleus is still receiving broad attention from many research groups all over the world. Historically, condensation reactions have commonly been used to prepare the pyrazolo[1,5-*a*]pyrimidine ring system from *NH*-3-aminopyrazoles and structurally diverse 1,3-*bis*-electrophilic reagents such as 1,2-allenic ketones, β -dicarbonyl compounds, alkoxymethylene- β -dicarbonyl compounds, β -enaminones, β -ketonitriles, β -haloenones, among others.³⁴⁻³⁶

Recently, microwave³⁷ and ultrasonic irradiation³⁸ were used to facilitate the reaction. However, some interesting and time-efficient metal-catalyzed, ionic, multicomponent, one-pot or microwave-assisted approaches have been recently proposed from various research groups and are presented here.

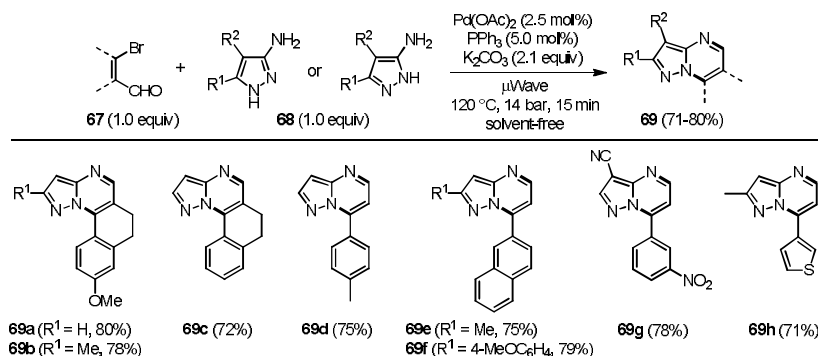
In the last decade, several eco-compatible methodologies have been described for the rapid access to highly functionalized pyrazolo[1,5-*a*]pyrimidines from *NH*-3-aminopyrazoles and various alkoxymethylene- β -dicarbonyl compounds by a domino aza-Michael-heterocyclic ring opening reaction.³⁹ In 2007, Quiroga, Portilla, and co-workers reported a solvent-free and time-efficient approach for the regioselective synthesis of 6-acetylpyrazolo[1,5-*a*]pyrimidines **63** containing benzoic acid residue. The synthesis was carried out in high yields from *NH*-3-aminopyrazoles **1** and 3-(3-oxo-2-benzofuran-1(3*H*)-ylidene)pentane-2,4-dione **61** via an aza-Michael addition of NH₂ group of **1** to C=C bond of substrate **61** with intramolecular ring opening of the furanone ring to give intermediate **62**. Then, pyrazolyl-enamine **62** was converted to pyrazolo[1,5-*a*]pyrimidines **63** by an intramolecular cyclocondensation (Scheme 13, above).⁴⁰ Afterward, the same group reported an analogous reaction but using 3-benzoyl-2-methyl-4*H*-chromen-4-one **64** as 1,3-*bis*-electrophilic substrate. In this work, 6-arylpayrazolo[1,5-*a*]pyrimidines **66** were obtained regioselectively in good yields via intramolecular opening of the γ -pyrone ring in an aza-Michael reaction to provide intermediates **65**. Notably, the cyclocondensation of **65** occurs with the participation of the carbonyl carbon at benzoyl group instead of carbonyl carbon at 2-hydroxybenzoyl group. The reason could be the electron-donating effect of the phenolic group which precludes this carbonyl carbon for the nucleophilic addition (Scheme 13, down).⁴¹



Scheme 13. Regioselective synthesis of polyfunctionally substituted pyrazolo[1,5-*a*]pyrimidines.

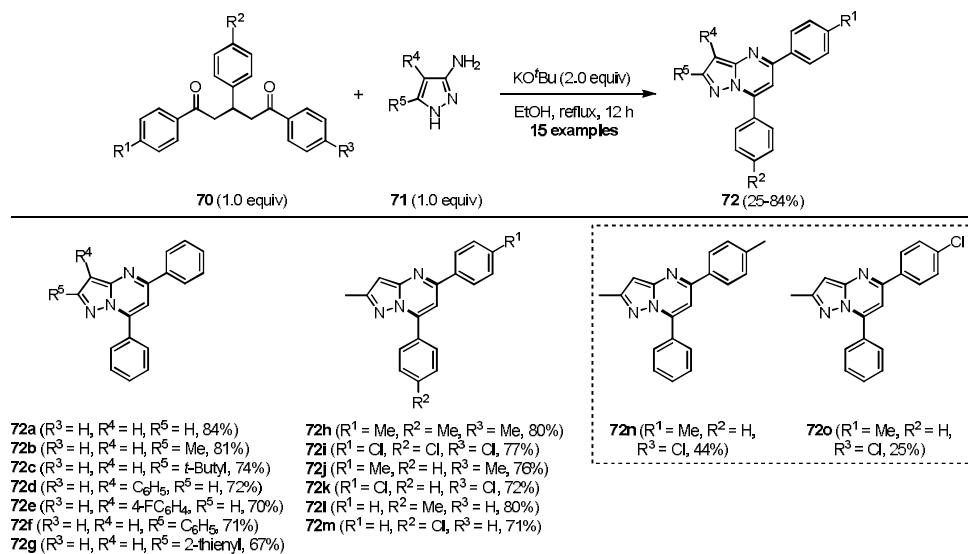
Palladium-catalyzed intramolecular coupling reactions clearly lead the way, and some elegant approaches to pyrazolo[1,5-*a*]pyrimidine derivatives have been reported in recent years.⁴² For example, in 2014, Shekarrao *et al.* reported the palladium-catalyzed microwave-assisted reaction of β -bromovinyl/aryl aldehydes **67** with different *NH*-3-aminopyrazoles **68** to regioselectively afford pyrazolo[1,5-*a*]pyrimidines **69** in good yields (Scheme 14).⁴³ The optimized reaction conditions of the catalytic version were Pd(OAc)₂, PPh₃ and K₂CO₃ as base under microwave irradiation at 700 Watt (120 °C and 14 bar) for 15 minutes in the

absence of solvent (Scheme 14). It is worth mentioning that, relative nucleophilicity of endo- and exocyclic nitrogen atoms in aminopyrazoles **68** is not so clear because controversial results can be found in the literature.^{44,45} Albeit metal-catalyzed reactions in presence of multiple heteroatoms are usually challenging owing to their tendency to form metal-heteroatom complexes, all the reactions were very efficient to afford pyrazolo[1,5-*a*]pyrimidines **69**. The reaction proceeds *via* initial formation of an imine between formyl group of **67** with free amino group of pyrazole **68**, followed by N-H tautomerization and intramolecular Buchwald-Hartwig C-N coupling cyclization reaction.



Scheme 14. Palladium-catalyzed synthesis of pyrazolo[1,5-*a*]pyrimidines under microwave irradiation.

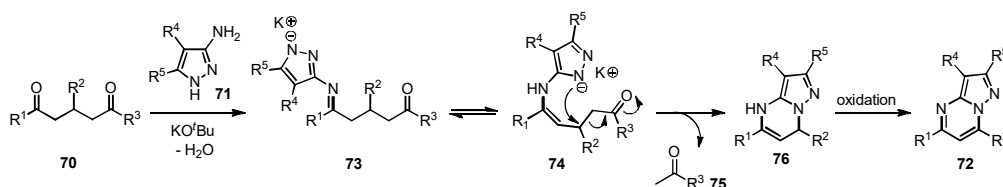
The development of new routes for selective cleavage of C-C bond is still remains as an important goal in organic chemistry due to the inert nature of the C-C bond.⁴⁶ Apart from 1,3-*bis*-electrophilic precursors, 1,5-dicarbonyl compounds constitute an interesting alternative for the formation of pyrazolo[1,5-*a*]pyrimidines by C-C bond cleavage reaction. For example, Saikia and co-workers reported a quite spectacular KO^tBu -promoted reaction of 1,5-dicarbonyl compounds **70** with various *NH*-3-aminopyrazoles **71** for the regioselective synthesis of polysubstituted pyrazolo[1,5-*a*]pyrimidines **72** (Scheme 15).⁴⁷



Scheme 15. KO^tBu -promoted regioselective synthesis of polysubstituted pyrazolo[1,5-*a*]pyrimidines.

Notably, the base-promoted cyclization reactions of symmetrical and unsymmetrical 1,5-dicarbonyl compounds **70** with pyrazoles **71** without substituents and substituted with methyl, *t*-butyl, phenyl and 4-fluorophenyl groups, proceeded efficiently under the optimized conditions to provide the corresponding products **72** in yields up to 84% (Scheme 15). It is important to note that the reaction of unsymmetrical 1-(4-chlorophenyl)-3-phenyl-5-(*p*-tolyl)pentane-1,5-dione **70** with *NH*-3-amino-5-methylpyrazole afforded a mixture of pyrazolo[1,5-*a*]pyrimidines **72n** and **72o** in 44% and 25% yield, respectively. They conclude that, phenyl ring substituted with electron-withdrawing group eliminated preferentially from the 1,5-dicarbonyl compound affording better yield of pyrazolo[1,5-*a*]pyrimidine **72n**.

From a mechanistic point of view, the reaction is believed to proceed *via* the condensation of ketone **70** with *NH*₂ group of **71** to form the imine, which undergoes deprotonation with KO^tBu to give the pyrazolide anion **73** (Scheme 16). Tautomerization of the imine **73** to the enamine **74**, followed by intramolecular nucleophilic attack of pyrazolide anion on the benzylic/allylic carbon affords intermediate **76** by elimination of one molecule of aryl methyl ketone **75**. Finally, the dihydroderivative **76** is spontaneously oxidized by aerial oxygen to the desired compound **72**.



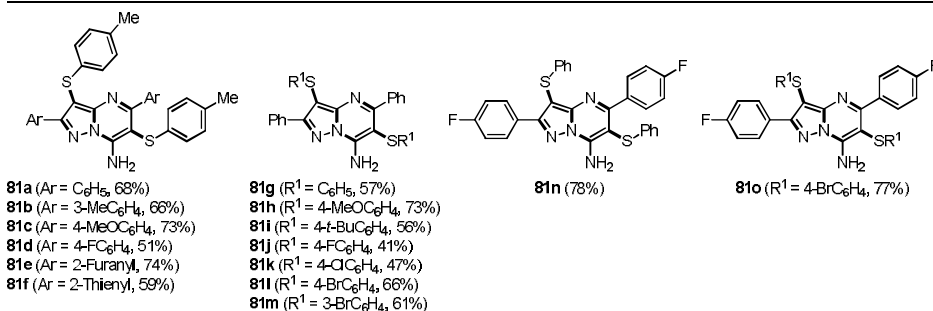
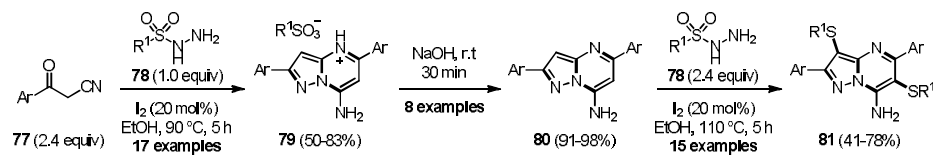
Scheme 16. Proposed mechanism of the KO^tBu-promoted reaction to yield pyrazolo[1,5-*a*]pyrimidines.

One of the most powerful stratagem for generating collections of small molecules by diversity-oriented synthesis (DOS) involves the sequencing of multicomponent reactions (MCRs) with subsequent chemical transformations such as post-functionalizations and cyclizations to generate heterocyclic scaffolds possessing increased structural diversity and molecular complexity.^{48,49} Aggarwal *et al.* described the *p*-TsOH catalyzed synthesis of 2,5-diarylpyrazolo[1,5-*a*]pyrimidin-7-amines from 3-aryl-3-oxopropanonitriles and hydrazine hydrate in a one-pot two-step manner.⁵⁰ Several of the functionalized pyrazolo[1,5-*a*]pyrimidin-7-amines exhibited potent *in vivo* anti-inflammatory activity by using the model of carrageenan-induced paw edema in rats. More recently, Sun and co-workers reported a novel I₂-catalyzed pseudo-three-component reaction of β -ketonitriles **77** with sulfonyl hydrazides **78** for the preparation of functionalized pyrazolo[1,5-*a*]pyrimidin-4-ium sulfonates **79** in a highly regioselective manner and yields up to 83%.⁵¹ The resulting sulfonate salts **79** reacted with 10% aqueous sodium hydroxide to give the free pyrazolo[1,5-*a*]pyrimidines **80** in excellent yields. Finally, sulfonyl hydrazides **78** were successfully used as a sulfonylating agent, enabling I₂-catalyzed pseudo-three-component reaction to provide fully substituted pyrazolo[1,5-*a*]pyrimidines **81** *via* direct C(sp²)-H bond functionalization (Scheme 17).

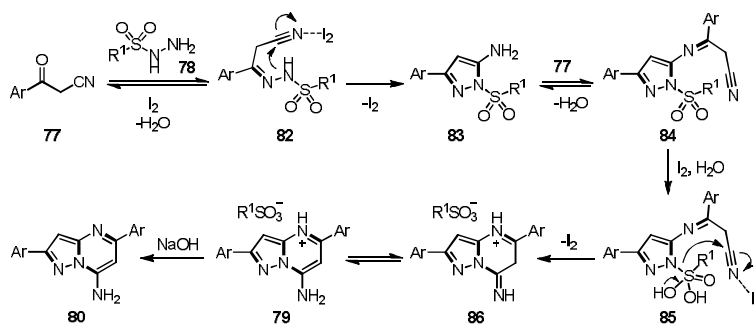
A plausible mechanism for these reactions would involve the I₂-catalyzed nucleophilic attack of sulfonyl hydrazides **78** to the CN group of β -ketonitriles **77** to generate *in situ* pyrazole intermediates **83**, followed by reacting with other β -ketonitrile molecule to afford imines **84**. Then, activated intermediates **85** undergo the cleavage of N-S bond and intramolecular 6-*exo-dig* cyclization to give pyrazolo[1,5-*a*]pyrimidin-4-ium sulfonates **79**, which were efficiently converted into compounds **80** in the presence of 10% aqueous sodium hydroxide (Scheme 18). The reaction of **80** with sulfonyl hydrazides **78** afforded disulphenylated pyrazolo[1,5-*a*]pyrimidines **81** by a mechanism that remains to be clarified (Scheme 17). This is the first reported method for the multicomponent synthesis of fully substituted pyrazolo[1,5-*a*]pyrimidines **81** *via* a sequential I₂-catalyzed bicyclization and disulphenylation pathway.

An interesting, albeit isolated, example concerns the cyclization-reduction-cyclization sequence introduced in 2016 by Castillo, Portilla, and co-workers for the microwave-assisted regioselective synthesis of structurally diverse pyrazolo[5,1-*b*]purines **93** in three steps and 60-70% overall yield (Scheme 19). Initially, the microwave-assisted solvent-free cyclization between *NH*-3-aminopyrazoles **1** and α -arylhydrazinyldene- β -ketonitriles **87** afforded the imine intermediates **88**, which reacted *via* an 6-*exo-dig*

cyclization-tautomerization sequence to provide the functionalized 6-(aryldiazanyl)pyrazolo[1,5-*a*]pyrimidin-7-amines **90** in good to excellent yields. The latter compounds were efficiently converted to their corresponding pyrazolo[1,5-*a*]pyrimidine-6,7-diamines **91** by a palladium-catalyzed reductive cleavage at ambient pressure. Finally, the microwave-assisted cyclocondensation reactions of **91** with various orthoesters **92** provided the tricyclic products **93** in very good yields exhibiting the pyrazolo[1,5-*a*]pyrimidine ring system.⁵²



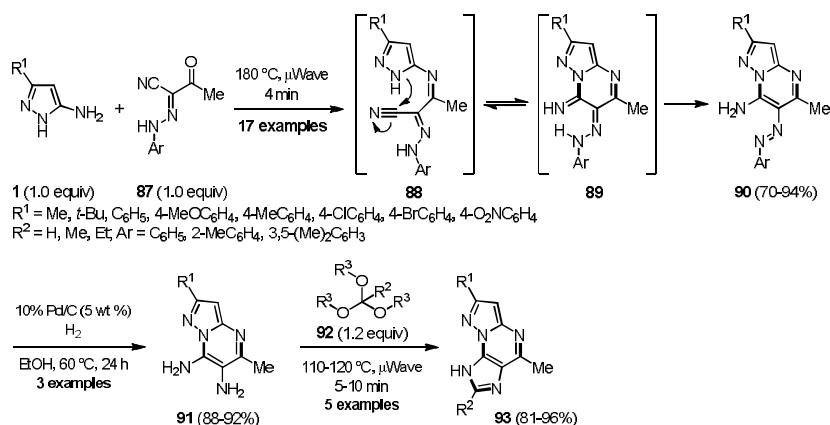
Scheme 17. I₂-Catalyzed multicomponent reactions for accessing functionalized pyrazolo[1,5-*a*]pyrimidines.



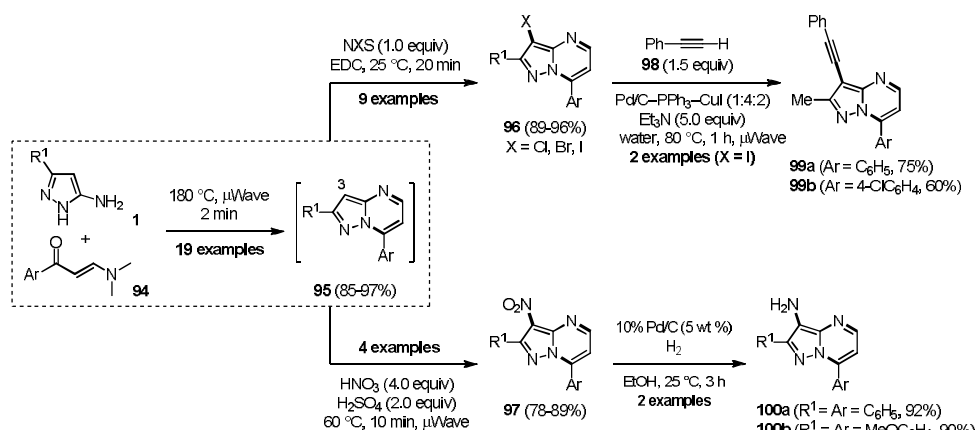
Scheme 18. Proposed mechanism for the synthesis of free pyrazolo[1,5-*a*]pyrimidines.

The microwave-assisted one-pot synthesis has proved to be an extremely powerful tool in organic chemistry because different chemical transformations and bond-forming steps can be carried out in a single pot. Thereby, time saving, operational simplicity and minimal chemical waste are achieved.⁵³ Despite the success of innumerable methods to synthesize the pyrazolo[1,5-*a*]pyrimidine ring system, we are surprised that its construction and subsequent functionalization in a single pot has remained largely unexplored. According to the results obtained in our previous work,⁵² we carry out the microwave-assisted reaction between aminopyrazoles **1** and β -enaminones **94** to obtain the expected pyrazolo[1,5-*a*]pyrimidines **95**, which were regioselectively halogenated and nitrated in the 3-position (Scheme 20).⁵⁴ Compounds **95** were obtained in high yields under solvent-free conditions at 180 °C for 2 min. We then examined the feasibility of carrying out reliable functionalization reactions in the same reactor without further isolation of **95** due to its almost quantitative formation. In this way, we developed an elegant and regioselective approach for the expeditious synthesis of 3-halo- and 3-nitropyrazolo[1,5-*a*]pyrimidines **96** and **97** in high yields with the

formation of three new bonds in a *one-pot* manner. These synthetic methods were distinguished by their short reaction times, operational simplicity, broad substrate scope, pot-economy and eco-compatibility in terms of energy and waste. Finally, some representative post-functionalization reactions were made to provide 3-alkynyl- and 3-aminopyrazolo[1,5-*a*]pyrimidines **99** and **100** in good yields under mild conditions.⁵⁴



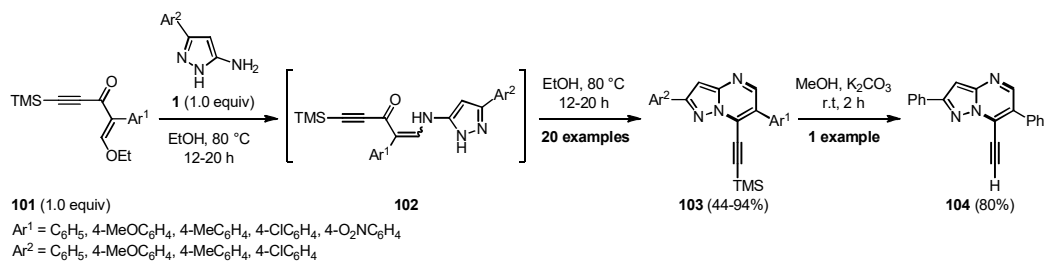
Scheme 19. Microwave-assisted synthesis of trisubstituted pyrazolo[5,1-*b*]purines.



Scheme 20. Microwave-assisted synthesis of 3-functionalized pyrazolo[1,5-*a*]pyrimidines.

Over the past several years, ethynylated heterocyclic compounds have emerged as versatile intermediates because alkynes have been successfully employed in numerous organic transformations such as click or cross-coupling reactions. Pursuing their efforts to develop a straightforward and metal-free procedure for the preparation of ethynylated pyrazolo[1,5-*a*]pyrimidines, Golubev and co-workers have recently reported the regioselective cyclization of variously substituted enynones **101** with *NH*-5-amino-3-arylpurazoles **1** for the preparation of 7-(trimethylsilylethynyl)pyrazolo[1,5-*a*]pyrimidines **103** in yields up to 94%, as depicted in Scheme 21.⁵⁵ The reaction outcome is not influenced by the substituent in **101** but depends on the type of aminopyrazole used. The reaction most probably begins with the Michael-type addition of NH₂ group of **1** to α,β -unsaturated carbonyl compound **101** and elimination of an ethanol molecule to afford enamine **102**, which further reacts by a tautomerization-cyclization-elimination sequence to give the ethynylated pyrazolo[1,5-*a*]pyrimidines **103**. It is important to mention that products of Michael-type addition to the triple bond were not detected, which indicated that the carbon atom adjacent to the ethoxy group is the most active

electrophilic center of enynes **101**. In order to demonstrate the possibility of further functionalization of the obtained compounds **103**, the triple bond was deprotected using potassium carbonate in MeOH at room temperature for 2 h to afford the pyrazolo[1,5-*a*]pyrimidine **104** containing a terminal acetylenic fragment in 80% yield. This synthetic methodology was distinguished by its broad substrate scope, functional groups tolerance, high regioselectivity, operational simplicity, no catalyst is used, and high isolated yields.



Scheme 21. Synthesis of 7-(trimethylsilylethynyl)pyrazolo[1,5-*a*]pyrimidines starting from enynes.

3.2. Pyrazolo[3,4-*b*]pyridines

Pyrazolo[3,4-*b*]pyridines are bicyclic heteroaromatic systems which allows for structural modifications at positions 1, 3, 4, 5, and 6 during ring-construction and subsequent functionalization steps. The first comprehensive review on this attractive heterocyclic core appeared in 1984.⁵⁶ However, the chemistry and biology of this *N*-heterocycles have undergone substantial developments since mid-1990s. To our knowledge, there is only one review available focusing on the latest development in their synthesis, which appeared in 2012.⁵⁷ In addition, other reviews on pyrazolo[3,4-*b*]pyridine kinase inhibitors and synthetic methodologies on the recent progress in the synthesis and functionalization of this *N*-heterocyclic system have appeared more recently.⁵⁸⁻⁶⁰ The pyrazolo[3,4-*b*]pyridine core is recognized as a privileged structural motif of drug-like molecules and commercially available drugs. For example, several drugs containing pyrazolo[3,4-*b*]pyridine scaffold such as Tracazolate, Etazolate, and Glicaramide are shown in Figure 4 with their approved activities.⁶¹⁻⁶³ Dodiya *et al.* classified the methods of synthesis of pyrazolo[3,4-*b*]pyridines in two main groups: (a) appropriately substituted pyridines onto which a pyrazole ring is annelated, and (b) suitably substituted pyrazoles onto which a pyridine ring is annelated. Further subdivisions have been provided with some specific reagents or reactions.⁵⁷ For example, the synthesis of pyrazolo[3,4-*b*]pyridines involves the reaction of *N*-substituted 5-aminopyrazoles with 1,3-*bis*-electrophilic reagents. Interestingly, the 1,3-*bis*-electrophile can be generated *in situ* by multicomponent reactions if this precursor is a α,β -unsaturated carbonyl compound, *i.e.* starting from aromatic aldehydes and active methylene compounds (AMCs).⁶⁴ However, these reactions proceeded without the participation of AMCs to afford *bis*-pyrazolo[3,4-*b*:4',3'-*e*]pyridines (BPs) by a *pseudo*-tricomponent reaction of aromatic aldehyde with two molecules of 5-aminopyrazole.⁶⁴⁻⁶⁶ Due to their wide spectrum of biological and pharmacological properties, the synthesis and functionalization of pyrazolo[3,4-*b*]pyridines is still receiving broad attention from many research groups all over the world. Therefore, some versatile and time-efficient multicomponent, one-pot and domino approaches under eco-compatible conditions have been recently reported from different research groups and are presented here.

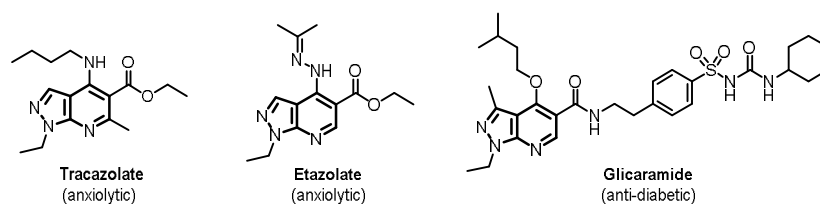
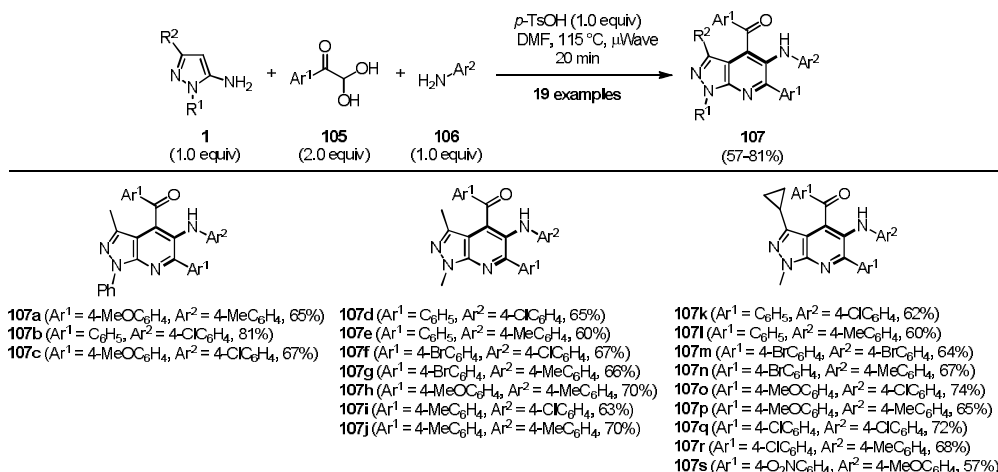


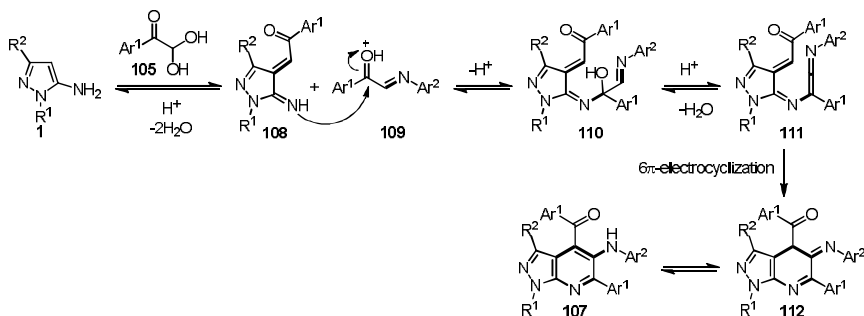
Figure 4. Drugs containing pyrazolo[3,4-*b*]pyridine scaffold.

Jiang and co-workers reported a chemoselective multicomponent reaction of 5-aminopyrazoles **1** with arylglyoxal monohydrates **105** and aromatic amines **106** for rapid access to fully substituted pyrazolo[3,4-*b*]pyridines **107** in good yields under microwave irradiation (Scheme 22).⁶⁷



Scheme 22. Four-component strategy for chemoselective synthesis of pyrazolo[3,4-*b*]pyridines.

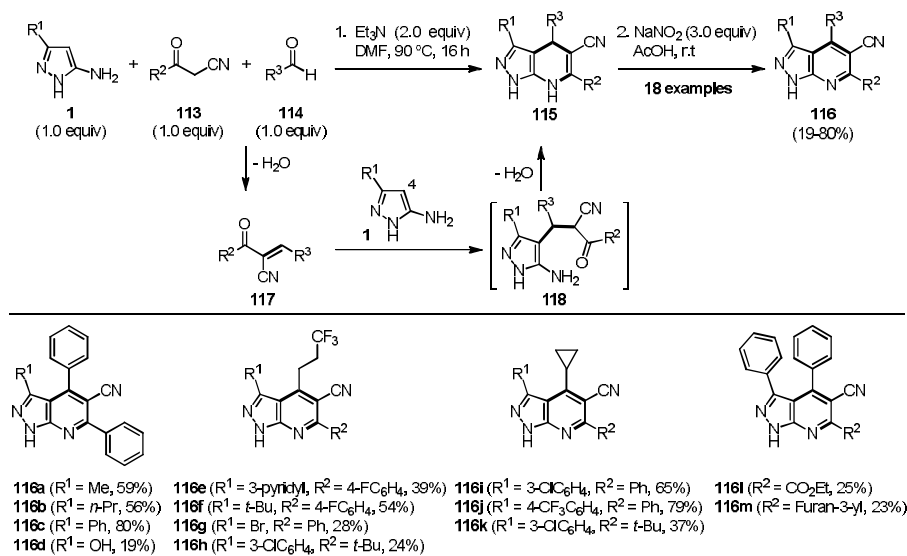
The reaction is likely to be initiated by a *p*-TsOH-promoted alkylation-dehydration sequence of **1** with the arylglyoxal **105** to generate enone intermediates **108**. After, α -ketoimines **109** reacted with the enone **108** by a chemoselective nucleophilic addition to provide α -hydroxyimines **110**, which were transformed into active allene intermediates **111**. The latter were then converted to expected products **107** via an intramolecular 6 π -electrocyclization-tautomerization sequence (Scheme 23). This is the first report on microwave-assisted synthesis of pyrazolo[3,4-*b*]pyridines by sequential cyclizations via a multicomponent domino reaction (MDR) without the use of any metal catalysts.



Scheme 23. Proposed mechanism to form pyrazolo[3,4-*b*]pyridines.

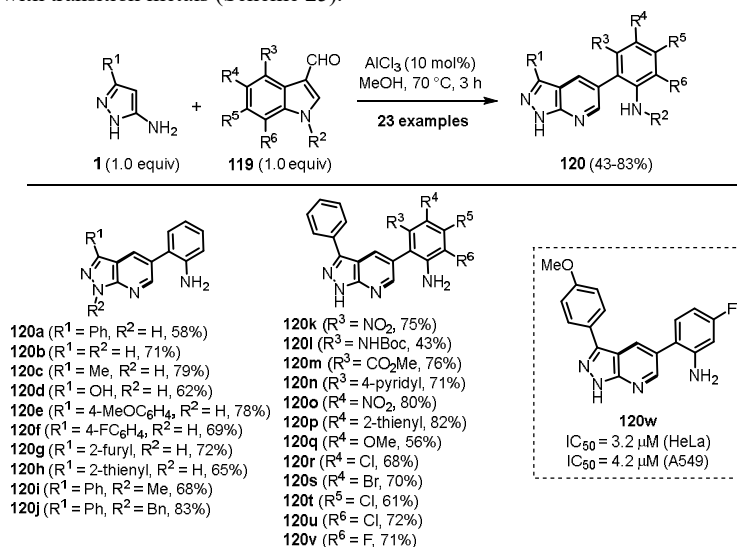
Hill reported a catalyst-free and one-pot synthesis of fully substituted 1*H*-pyrazolo[3,4-*b*]pyridines **116** based on a three-component approach between *NH*-5-aminopyrazoles **1**, β -ketonitriles **113** and aromatic/aliphatic aldehydes **114** in the presence of triethylamine to give 4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine intermediates **115**, which were subsequently oxidized with sodium nitrite in acetic acid at room temperature to afford bicyclic products **116** in acceptable yields, high regioselectivity, and the formation of three new bonds in a one-pot two-step manner (Scheme 24).⁶⁸ The reaction was initiated by a Knoevenagel condensation between 3-oxopropanenitriles **113** and aldehydes **114** to give acrylonitrile intermediates **117**, which underwent a Michael addition of C-4 of **1** to form

intermediates **118**. Finally, a selective dehydrative cyclization followed by an oxidation step afforded the desired *1H*-pyrazolo[3,4-*b*]pyridines **116**. The salient features of this protocol are mild reaction conditions, non-isolation of 4,7-dihydro-*1H*-pyrazolo[3,4-*b*]pyridine intermediates, and *NH*-5-aminopyrazoles did not require N1 protection to achieve the desired regiochemical outcome.



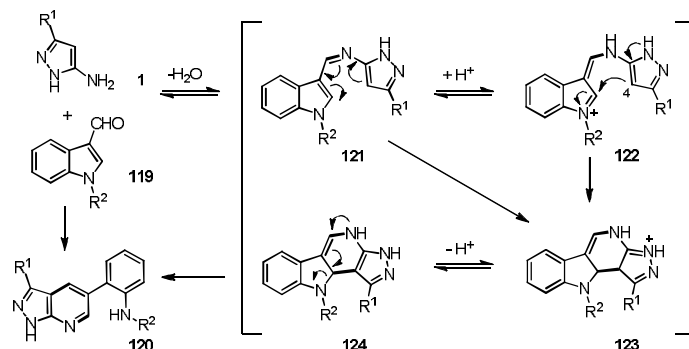
Scheme 24. Multicomponent approach to fully substituted *1H*-pyrazolo[3,4-*b*]pyridines.

Lee and Park reported an efficient AlCl_3 -catalyzed synthesis of heterobiaryl pyrazolo[3,4-*b*]pyridines **120** from *NH*-5-aminopyrazoles **1** and indole-3-carboxaldehydes **119** by the indole ring opening without using catalysis with transition metals (Scheme 25).⁶⁹



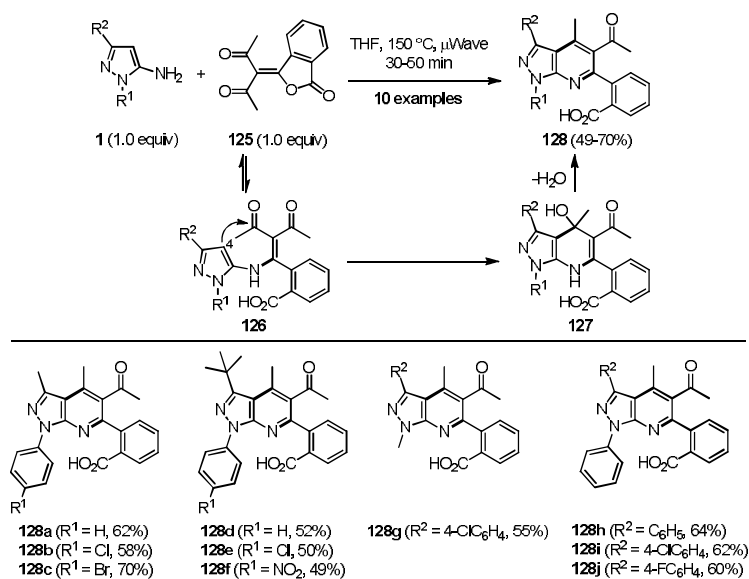
Scheme 25. Synthesis of heterobiaryl pyrazolo[3,4-*b*]pyridines.

The optimized reaction conditions were AlCl_3 (10 mol%) in methanol at reflux for 3 h to provide functionalized compounds **120** in good yields and excellent regioselectivity. A plausible mechanism for these reactions would involve the formation of the imine **121**, followed by intramolecular cyclization either *via* a pericyclic rearrangement of intermediate **121** or by nucleophilic addition by the C-4 of pyrazole on the iminium electrophile **122** to provide a tetracyclic intermediate **123** (Scheme 26). The latter would then undergo rearomatization, leading to the opening of the indole ring to form the pyrazolo[3,4-*b*]pyridine core **120**. The product **120w** showed excellent antiproliferative activity with IC_{50} values of 3.2 and 4.2 μM in HeLa and A549 cell lines, respectively (Scheme 25).



Scheme 26. Plausible mechanism to form heterobiaryl pyrazolo[3,4-*b*]pyridines *via* the indole ring opening.

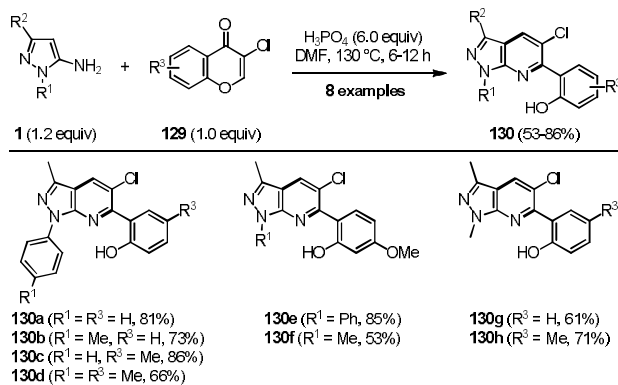
As previously demonstrated by us and others, the domino Michael–heterocyclic ring opening sequence from heterocyclic α,β -unsaturated carbonyl compounds allows an efficient access to highly functionalized pyrazolo[3,4-*b*]pyridines.⁷⁰ In 2017, Portilla and co-workers developed a microwave-assisted regioselective approach to fully substituted pyrazolo[3,4-*b*]pyridines **128** from 5-aminopyrazoles **1** and 3-(3-oxo-2-benzofuran-1(3*H*)-ylidene)pentane-2,4-dione **125**, based on a domino aza-Michael-cyclization-dehydration sequence (Scheme 27).⁷⁰



Scheme 27. Microwave-assisted synthesis of pyrazolo[3,4-*b*]pyridines.

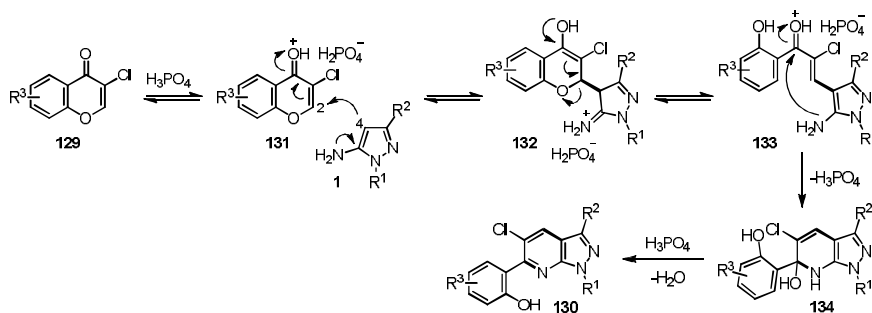
In the course of the reaction, the intermediate pyrazolyl-enamine **126** is formed following a reversible Michael-furanone ring opening reaction, and its *in situ* intramolecular nucleophilic attack by the C-4 position of pyrazole ring on the carbonyl carbon afforded the 1,4-dihydropyridine intermediate **127**. The latter underwent dehydration reaction to yield pyrazolo[3,4-*b*]pyridines **128** in moderate yields (up to 70%), high regioselectivity and short reaction times under catalyst-free conditions (Scheme 27). The results obtained allowed us to establish that the steric effect in the 1,3-*bis*-electrophilic reagent and the temperature are crucial factors in determining the course of this reaction. This methodology is the second reported example of a domino reaction using the 1,3-*bis*-electrophile **125**, which could be used to synthesize diverse polyfunctionally substituted heterocyclic compounds starting from different hetarylamines.

In 2018, Miliutina and co-workers disclosed a novel and efficient domino reaction to synthesize diversely substituted pyrazolo[3,4-*b*]pyridines **130** in 53-86% yield starting from 5-aminopyrazoles **1** and 3-chlorochromones **129** in the presence of phosphoric acid (Scheme 28).⁷¹



Scheme 28. Convenient synthesis of functionalized pyrazolo[3,4-*b*]pyridines.

It is important to note that better regioselectivity and higher yields were observed when 3-chlorochromone was used as compared to the use of 3-bromo- and 3-iodochromone. In fact, the reaction with 3-bromochromone resulted in a decrease of the regioselectivity to produce a mixture of various products. Moreover, 3-iodochromone loses its iodine atom during the reaction to afford products identical to those obtained when 3-unsubstituted chromone was used. The reaction is likely to be initiated by protonation of the carbonyl oxygen of **129** in the presence of phosphoric acid to give intermediates **131** containing an electrophilic carbon C-2, which underwent a nucleophilic attack of C-4 of **1** and subsequent cleavage of the chromone ring system to obtain α,β -unsaturated ketones **133** (Scheme 29). The latter were then converted to pyrazolo[3,4-*b*]pyridines **130** *via* an acid-catalyzed 6-*exo-dig* cyclization-dehydration sequence.

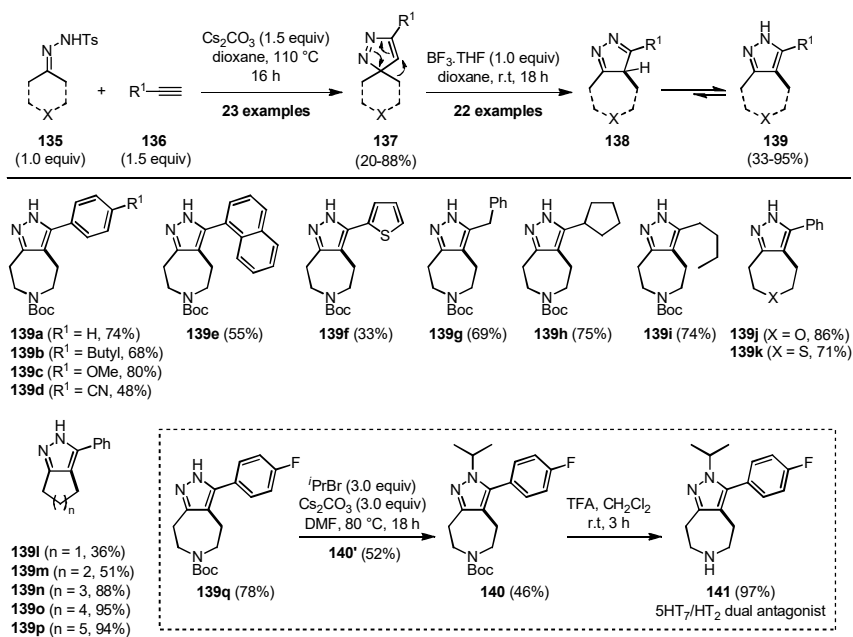


Scheme 29. Plausible mechanism for the synthesis of pyrazolo[3,4-*b*]pyridines.

These compounds **130** were tested against both human (*h*-) and rat (*r*-) isozymes and it was observed that most of the derivatives inhibit human ecto-5'-nucleotidases (*h*-e5'NT) at a very low concentration. Particularly, compound **130d** was recognized as the most potent inhibitor of *h*-e5'NT, exhibiting an inhibitory value ($IC_{50}=0.32 \mu\text{M}$) which was 131 fold better as compared to the reference standard, sulfamic acid ($IC_{50}=42.1 \mu\text{M}$), as shown in Scheme 28.

3.3. Synthetic utilities of fused pyrazoles

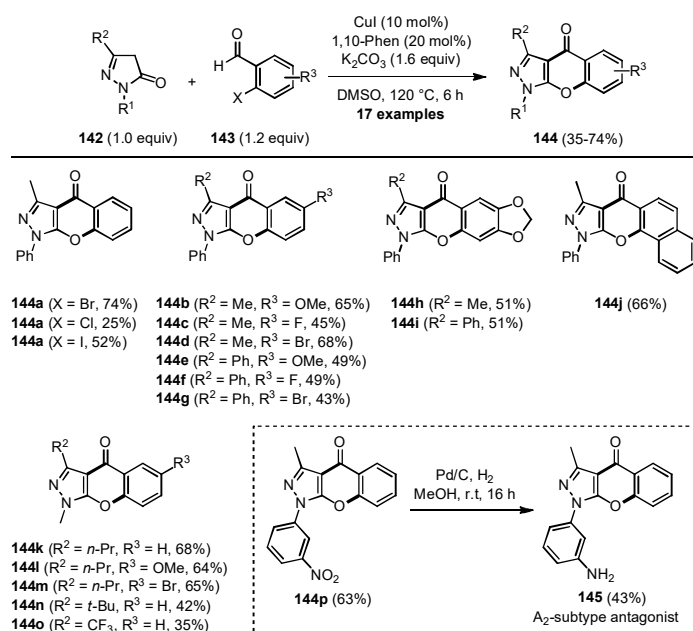
Analysis of database of U.S. FDA approved drugs reveals that 59% of unique small molecule drugs contain a nitrogen heterocycle.⁷² In this context, the chemistry of pyrazole derivatives has played an important role in drug design and medicinal chemistry due to their broad range of therapeutic and pharmacological properties.⁷³⁻⁷⁶ Albeit great endeavors have been devoted for the preparation of pyrazolo-fused heterocycles, the development of new methods to improve synthetic efficiency and structural diversity still remains as an important and challenging goal for the organic and medicinal chemistry. In fact, the importance of some heteroaromatic fused pyrazoles was evidenced in the previous two sections (3.1 and 3.2); however, saturated fused pyrazoles have also demonstrated a broad range of biological activities, but their preparation is not always efficient and straightforward. In this way, Merchant and co-workers prepared ring-expanded fused pyrazoles **139** by a two-step synthetic sequence including a [3+2]-cycloaddition-sigmatropic rearrangement (Scheme 30).⁷⁷ Thus, the cycloaddition reaction between terminal alkynes **136** and diazo intermediates generated *in situ* from bench-stable tosylhydrazones **135** under the optimized conditions provided the functionalized 3,3-spirocyclic pyrazoles **137** with yields up to 88%. The latter was converted to the fused pyrazoles **139** by a BF_3 -mediated sigmatropic rearrangement with concomitant one-carbon expansion of the saturated ring in yields up to 95%. In order to demonstrate the utility of this elegant methodology, the synthesis of 5HT₇/HT₂ dual antagonist **141** was performed.⁷⁸ Thus, bicyclic compound **139q** was *N*-alkylated to give a 46% of the desired regioisomer **140**, along with a 52% yield of the undesired regioisomer **140'**. Next, removal of the Boc protecting group with trifluoroacetic acid (TFA) afforded 5HT₇/HT₂ dual antagonist **141** in almost quantitative yield.



Scheme 30. Synthesis of fused pyrazoles *via* sigmatropic rearrangement of spirocyclic pyrazoles.

This two-step approach allows the synthesis of saturated polycyclic frameworks incorporating unusual ring sizes, which are typically challenging to obtain using conventional procedures.

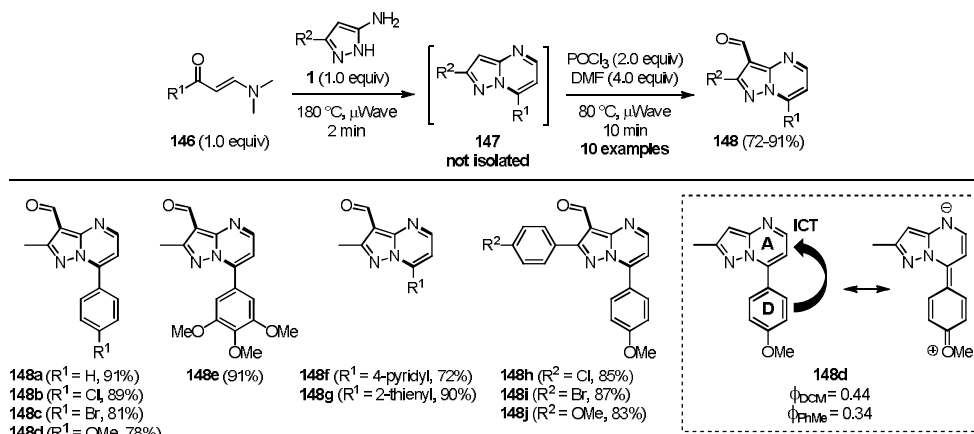
Over the last decade, the cross dehydrogenative coupling (CDC) has proven to be one of the most important methods for the selective construction of C-C bonds by directly connecting two different C-H bonds under oxidative conditions.⁷⁹ The intramolecular CDC processes provide privileged fused compounds containing a ketone functionality. However, for such intramolecular transformations, the necessary precursor needs to be presynthesized. Recently, Obulesu *et al.* reported a copper-catalyzed tandem O-arylation-oxidative cross coupling process using 2,4-dihydro-3H-pyrazol-3-ones **142** and various 2-haloaryl aldehydes **143** for the preparation of chromone fused pyrazoles **144** in moderate to good yields under aerobic conditions (Scheme 31).⁸⁰ The optimized reaction conditions of this tandem process were CuI (10 mol%) as a catalyst, 1,10-Phen (20 mol%) as a ligand and K₂CO₃ in DMSO at 120 °C for 6 h in presence of air as oxidizing agent. It is noteworthy that the synthetic utility of this copper-catalyzed tandem process has been demonstrated with the synthesis of an A₂-subtype selective adenosine receptor antagonist **145** in only two steps (Scheme 31).⁸¹



Scheme 31. Synthesis of chromone fused pyrazoles from pyrazol-3-ones and 2-haloaryl aldehydes.

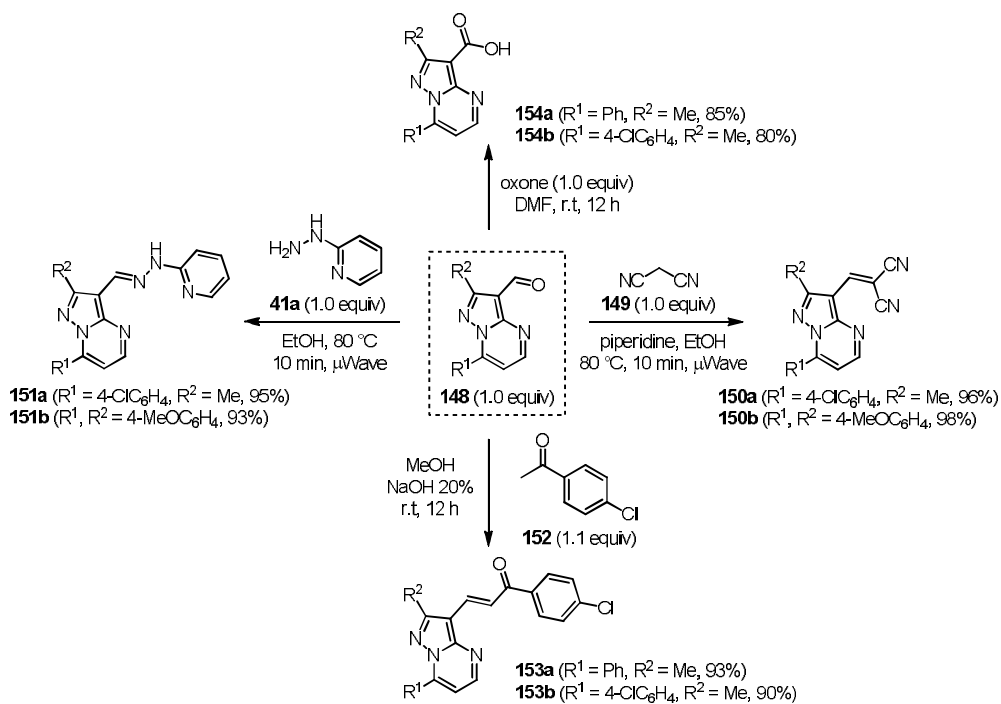
In spite the existence of numerous pyrazolo[1,5-*a*]pyrimidines synthesis, efficient and regioselective methods which can introduce a broad range of functional groups such as hydrazone, carboxyl and enone on the pyrazole ring by a single-step or one-pot procedure have been poorly explored. From the viewpoint of environmental sustainability in organic synthesis, developing operationally simple, time-efficient and additive-free methods for preparing 3-functionalized pyrazolo[1,5-*a*]pyrimidines in a one-pot manner is highly desirable. More recently, Castillo, Tigreros, and Portilla reported a regioselective one-pot approach for the expeditious synthesis of 3-formylpyrazolo[1,5-*a*]pyrimidines **148** under microwave irradiation (Scheme 32).^{10c} The synthesis proceeds by a microwave-assisted cyclization between β -enaminones **146** and *NH*-3-aminopyrazoles **1** to provide the pyrazolo[1,5-*a*]pyrimidine intermediates **147**, which were successfully engaged in a Vilsmeier-Haack reaction with an iminium salt under microwave irradiation to give the corresponding heteroaromatic aldehydes **148** in good to excellent yields. Since pyrazolo[1,5-*a*]pyrimidines **148** have shown an interesting fluorescence, photophysical properties of four 2-methyl derivatives **148a** and **148d-f** with different acceptor (A) or donor (D) groups were studied.

Interestingly, the fluorophore (D-A) **148d** exhibited the highest fluorescence intensity with quantum yields (ϕ_F) up to 44% due to the presence of a strong electron-donating group as 4-methoxyphenyl that favors a higher intramolecular charge transfer (ICT) (Scheme 32).⁸²



Scheme 32. Regioselective one-pot synthesis of 3-formylpyrazolo[1,5-*a*]pyrimidines under microwave irradiation. Relative quantum yields were obtained with anthracene ($\phi_F=0.28$ in ethanol) as reference.

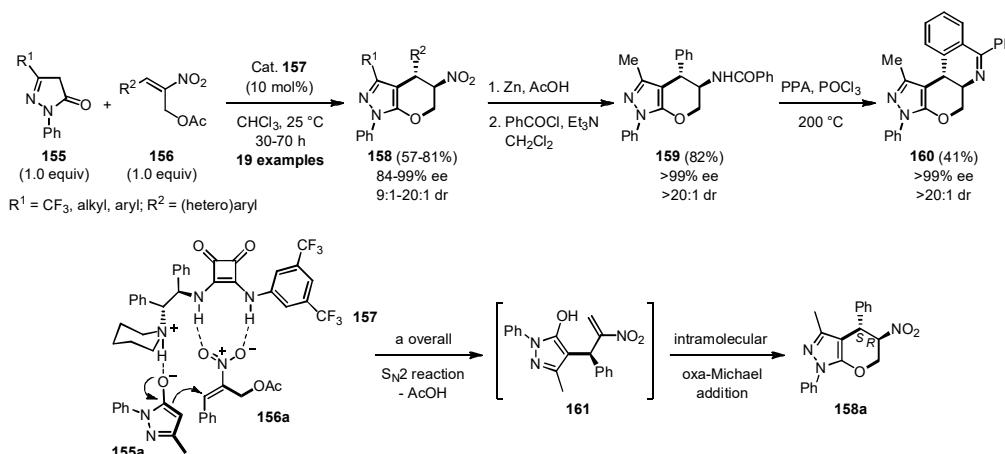
Further chemical manipulations of heteroaromatic aldehydes **148** by environmentally friendly procedures were also reported (Scheme 33).



Scheme 33. Synthesis of post-functionalized pyrazolo[1,5-*a*]pyrimidines.

Heteroaryldehydes **148** suffered condensation reactions with diverse reagents such as malononitrile, 2-pyridylhydrazine and 4-chloroacetophenone to afford dicyanovinyl **150**, hydrazone **151** and enone **153** derivatives respectively, in excellent yields. The novel functional derivatives **150** and **151** could be used as fluorescent probes for selective recognition of cyanide or for the detection of metal ions respectively, similar to recent reports published by us.⁸³ It is remarkable that compounds **148a,b** were efficiently oxidized to their carboxylic acids **154a,b** in good yields by a metal-free process using Oxone as oxidizing agent in DMF at room temperature (Scheme 33).

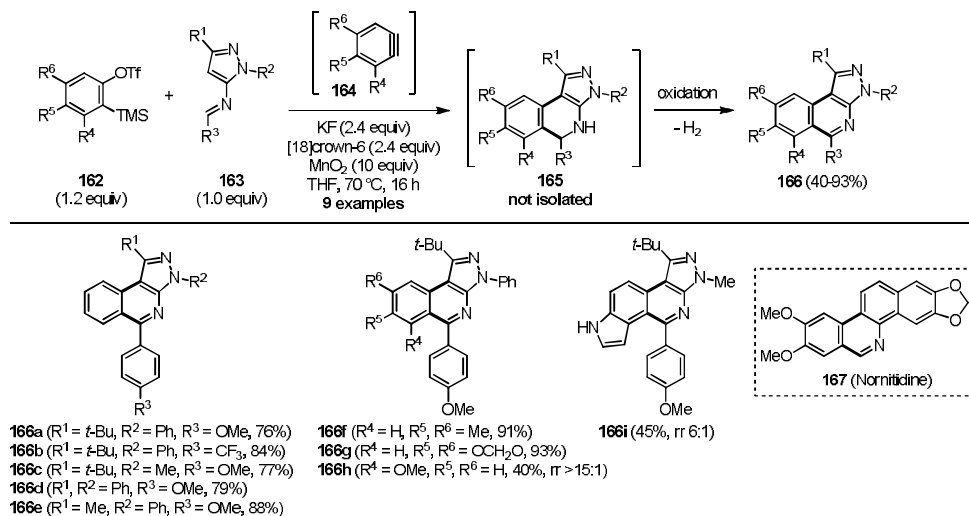
Alternatively, the organocatalytic asymmetric formal [3+3]-annulation approach to highly functionalized tetrahydropyrano[2,3-*c*]pyrazoles **158** was proposed recently by Zheng and co-workers involving the Michael-elimination-Michael cascade reaction (Scheme 34).⁸⁴ In the presence of a catalytic amount of (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine derived tertiary amine-squaramide **157**, 1,3-*bis*-nucleophilic pyrazolin-5-ones **155** and 1,3-*bis*-electrophilic Morita-Baylis-Hillman (MBH) acetates of nitroalkenes **156** afforded the tetrahydropyrano[2,3-*c*]pyrazoles **158** containing two adjacent stereogenic centers in good yields, high *trans*-selectivities, and excellent enantioselectivities. A plausible mechanism is shown in Scheme 34. Initially, an enolate is formed *via* the deprotonation of **155a** by the tertiary amine group of the bifunctional squaramide catalyst **157**. Simultaneously, nitroallylic acetate **156a** was activated by hydrogen bonding interactions between the squaramide moiety and the nitro group. The mechanism proceeds by a S_N2'-type reaction involving the Michael addition of enolate on the *Re* face of the nitroolefin, followed by the elimination of the acetate group to generate the nitroolefin intermediate **161**. Finally, intramolecular oxa-Michael addition with the aid of a bifunctional squaramide catalyst afforded the tetrahydropyrano[2,3-*c*]pyrazole **158a**. Moreover, the tetrahydropyrano[2,3-*c*]pyrazole **158a** could be transformed into biologically important fused dihydroisoquinoline **160** by a sequence of nitro group reduction, benzylation, and intramolecular dehydration. These chemical transformations proceeded without any appreciable loss in the enantio- and diastereoselectivity.



Scheme 34. Proposed reaction mechanism for the construction of tetrahydropyrano[2,3-*c*]pyrazole scaffold *via* an organocatalyzed formal [3+3]-annulation.

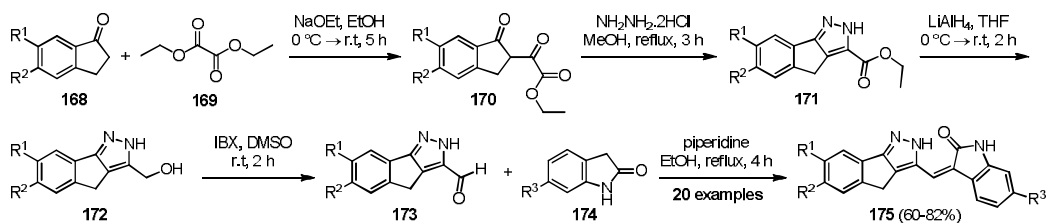
Multiple bond-forming transformations (MBFTs) allowing for the sequential creation of two or more carbon-carbon bonds in a single chemical operation are highly valuable in synthetic organic chemistry.^{85,86} In the course of their studies on the total synthesis of the naturally occurring benzo[*c*]phenanthridine alkaloid Normitidine **167**, Castillo, *et al.* reported a flexible and time-efficient approach to diversely functionalized heteropolycyclic products exhibiting a pyrazole core from electron-rich *N*-aryl imines and arynes, based on an aza-Diels-Alder cycloaddition-aromatization cascade reaction (Scheme 35).⁸⁷ In the course of the reaction, the 1,2-dihydroisoquinoline intermediates **165** were formed following a normal electron-demand aza-Diels-Alder [4+2]-cycloaddition between easily accessible electron-rich *N*-pyrazolyl aldimines **163** and

benzynes **164**, generated *in situ* by fluoride-induced 1,2 elimination from the *ortho*-silylated aryltriflates **162**, and their subsequent aromatization in the presence of excess MnO₂ to afford the desired products **166** in good yields and with good to excellent regioselectivities using non-symmetric arynes (regioisomer ratios from 6:1 to >15:1) as shown in Scheme 35. According to DFT calculations, the relative nucleophilicities of the nitrogen atom and the *N*-aryl moiety are essential factors that govern the periselectivity ([2+2] vs. [4+2]) of the cycloaddition reactions between arynes and 2-aza-dienes.



Scheme 35. Synthesis of pyrazole-fused isoquinolines *via* the oxidative aryne aza-Diels-Alder reaction.

Also of interest is the work from the groups of Kamal and Kumar, in studies on the synthesis and biological evaluation of indano-pyrazole conjugates as promising anti-mitotic agents that target microtubules (Scheme 36).⁸⁸ Initially, substituted indanones **168** reacted with diethyl oxalate **169** in presence of sodium ethanolate in ethanol to give the indanones 2-(2-ethoxy-2-oxoacetyl)substituted **170**, followed by a cyclocondensation with NH₂NH₂·2HCl to provide the fused pyrazole 3-ethoxycarbonylsubstituted **171**. Next, reduction of these esters by lithium aluminum hydride in tetrahydrofuran afforded primary alcohols **172**, which were selectively oxidized to the respective heteroaryl aldehydes **173** using 2-iodoxybenzoic acid (IBX) in dimethylsulfoxide. With **173** in hand, the key Knoevenagel condensation proceeded with oxindoles **174** under basic catalysis to afford the 1,4-dihydroindeno[1,2-*c*]pyrazole linked oxindole analogues **175** with yields up to 82%. Moreover, indano-pyrazole conjugates **175a-c** showed excellent cytotoxicity with IC₅₀ values ranging between 1.33 to 5.10 μM as shown in Table 1. Furthermore, detailed biological assays showed that there was accumulation of mitotic cells in G2/M phase, disruption of microtubule network and increase in the G2/M checkpoint proteins (Cyclin B1 and CDK1). It is important to note that the molecular docking analysis demonstrated that these congeners occupy the colchicine binding pocket of the tubulin.



Scheme 36. Synthesis of 1,4-dihydroindeno[1,2-*c*]pyrazole linked oxindole analogues.

Table 1. *In vitro* antiproliferative activity of 1,4-dihydroindeno[1,2-*c*]pyrazoles.

Compound	R ¹	R ²	R ³	IC ₅₀ (μM) ^a			
				HeLa ^b	A549 ^c	MDA-MB-231 ^d	HEK-293 ^e
175a	OMe	OMe	H	2.16	2.92	3.45	4.36
175b	OMe	OMe	OMe	2.58	3.43	4.14	5.10
175c	OMe	OMe	Cl	1.33	2.44	2.08	2.97
CA4 (Standard)	-	-	-	1.43	1.15	0.92	1.73

^aConcentration required to inhibit 50% of cell growth. ^bCervical cancer, ^cLung cancer, ^dBreast cancer and ^eNormal human embryonic kidney cell line.

4. Conclusion

To sum up, we have described some recent advances in the synthesis of new pyrazole derivatives, which were mainly based on topics of interest and studies conducted by our group. A remarkable description in the synthesis and generalities of some functionalized pyrazoles and relevant fused pyrazoles was achieved. Emphasis was placed on aminopyrazoles and formylpyrazoles as well as on the fused systems pyrazolo[1,5-*a*]pyrimidines and pyrazolo[3,4-*b*]pyridines. Pyrazoles and their fused derivatives are obtained mainly by cyclocondensation reactions of 1,3-*bis*-electrophiles with hydrazine derivatives or with 5-aminopyrazoles, respectively. All functionalized pyrazoles explored herein occupy a noticeable place in organic and medicinal chemistry, however formylpyrazoles are less popular than aminopyrazoles, and within each group (amines or aldehydes), the 4-amino and the 3(5)-formyl derivatives are less frequent and most of the existing reports on these systems are patents. On the other hand, pyrazolo[1,5-*a*]pyrimidines are more popular than pyrazolo[3,4-*b*]pyridines, but both fused systems are of significant biological interest and have recently acquired physicochemical relevance due to electron-rich properties of the pyrazolic ring. In general, pyrazolo[1,5-*a*]pyrimidines synthesis involves the interaction between *NH*-3-aminopyrazoles with 1,3-*bis*-electrophiles, while pyrazolo[3,4-*b*]pyridines are obtained using *N*-substituted 5-aminopyrazoles. Several structural and synthetic aspects of pyrazoles and their fused systems, implemented as part of novel hybrid molecules allows envisioning a very bright future of this structural moiety in chemical synthesis, biochemical and physicochemical research.

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