RECENT ADVANCES IN AMINOPYRAZOLES SYNTHESIS AND FUNCTIONALIZATION

DOI: http://dx.medra.org/10.17374/targets.2018.21.322

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Abstract. *Aminopyrazoles represent an important class of heterocycles in medicinal chemistry due to their numerous biological activities. This chapter aims to cover the synthesis and reactivity of aminopyrazoles since 2009. Specific regio and chemoselectivity problematics have been emphasized.*

Contents

1. Introduction

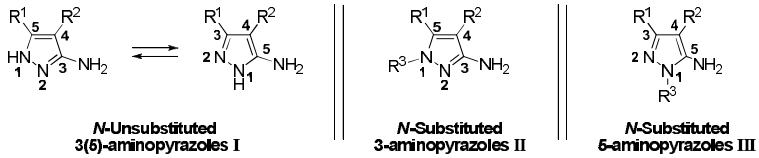
Aminopyrazoles, a subset of the pyrazoles family,[1] are heterocyclic compounds that exhibit a great interest from the scientific community due to their significant biological properties. Indeed, this motif is found in numerous molecules associated with significant agricultural or pharmaceutical properties. Those activities have been the subject of recent review articles.[2]

Aminopyrazoles are five membered-heterocycles containing two adjacent endocyclic nitrogen atoms and one exocyclic amino group. Those features induce some specificity regarding the synthesis and the reactivity of this scaffold. In particular, the synthetic chemist has to face chemo and regioselectivity issues that are peculiar to aminopyrazoles. A bibliographical study devoted to the sole synthesis of 5-aminopyrazoles was published in 2011[3] while the ever-growing chemistry of aminopyrazoles has been collected in the 2009 review by Anwar.[4]

This chapter covers the development associated with the singular aspects of aminopyrazoles chemistry since 2009 up to November 2017. More precisely, recently reported synthesis of the aminopyrazole core from linear precursors through annelation or cylization reactions have been surveyed. Transition metal-catalyzed monofunctionalizations of aminopyrazoles, which have not been reviewed before are also presented herein. Finally, difunctionalizations of aminopyrazoles leading to fused bicyclic systems that have been the subject of intensive developments are also surveyed in this chapter.

2. Synthesis of 3-(5)-aminopyrazoles

3-(5)-Aminopyrazoles are generally obtained by the condensation of an hydrazine and a 1,3-dielectrophilic compound in which one of the electrophilic functional group is a nitrile. The use of hydrazine itself leads to the tautomeric *N*-unsubstituted 3- and 5-aminopyrazoles **I** (Scheme 1). The use of monosubstituted hydrazines affords the regioisomeric *N*-substituted 3-aminopyrazoles **II** and 5-aminopyrazoles **III**. It is known that the main factor controlling this reaction is the nucleophilicity of the hydrazine nitrogen atoms, with the 1,2-addition of the primary amino group occurring preferentially on the most electrophilic position under neutral or acidic conditions.[5]



Scheme 1

2.1. Reaction of β-ketonitriles with hydrazines

One of the most common method to synthesize 3-(5)-aminopyrazoles involves the condensation of hydrazine with β-ketonitriles. In a first step, an hydrazone is generated by a nucleophilic attack of the hydrazine onto the carbonyl group. Then, addition of the other hydrazine nitrogen atom onto the nitrile carbon atom allows the cyclization that lead to the expected heterocycle.[6] Reaction based on the use of hydrazine will be reported first and then regioselectivities observed on the use of monosubstituted hydrazines will be discussed.

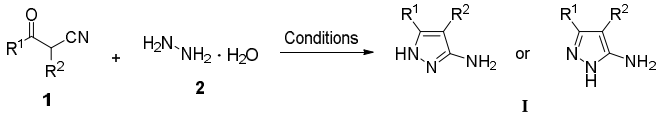
2.1.1. With the hydrazine

The condensation of β-ketonitriles **1** with hydrazine hydrate **2** has been widely used for the preparation of *N*-unsubstituted 3-(5)-aminopyrazoles **I** (Table 1) Neutral conditions[7,9] (entries 1-3) and acidic ones[10,11] (entries 4-6) were reported in alcoholic solvents. The use of microwaves activation was reported to shorten the reaction time up to 10 min instead of the 1-16 h required under classical thermal activation.[12]

2.1.2. With monosubstituted hydrazines

Rao reported the regioselective synthesis of 5-aminopyrazoles **III** upon reacting β-ketonitriles **1** with monosubstituted hydrazines **3** in refluxing EtOH (Table 2).[13] Uneventfully, methylhydrazine sulfate required the addition of a base (entry 1), while phenylhydrazine reacted in neutral conditions (entry 2).

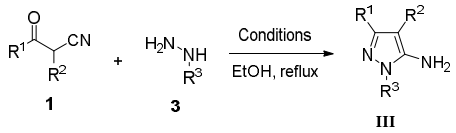
Table 1



1 **2** **I**

Entry	R^1	R^2	Conditions	Yield (%)	Ref
1	Ph	F	*i*-PrOH, rt, 1 h	72	7
2	Ph	F	EtOH, rt, 16 h	50	8
3	C_6H_4*p*-OMe	H	EtOH, 100 °C, 6 h	77	9
4	H, OBn, OMe	H	EtOH, AcOH, 75 °C, 3 h	96-99 (3 examples)	10
5	Ar	C_6H_4*p*-OMe	EtOH, HCl, 90 °C, 14 h	91-97 (4 examples)	10
6	C_6H_4*p*-F, C_6H_4*p*-I	CH_2CONEt_2	EtOH, AcOH, 80 °C, 8 h	83-88 (2 examples)	11

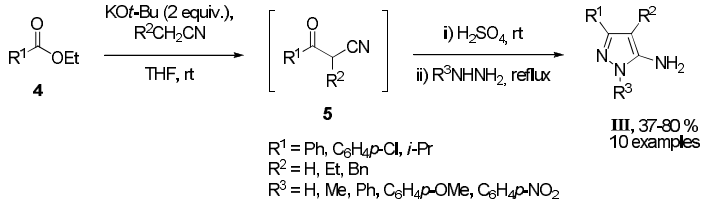
Table 2



1 **3** **III**

Entry	R^1	R^2	R^3	**3**	Conditions	Yield (%)	Ref
1	Ph	H	Me	$MeNHNH_2.H_2SO_4$	NEt_3 (1 equiv.), 2 h	75 %	13
2	Ph	H	Ph	$PhNHNH_2$	6 h	70 %	13

Yoon and coworkers described in 2015 the direct synthesis of pyrazoles **III** from esters **4** *via* two sequential reactions (Scheme 2).[14] A *tert*-butoxide-assisted Claisen condensation allows the access to β-ketonitriles intermediates **5**, followed by hydrazine addition that leads to the formation of various 5-aminopyrazoles **III**. During the optimization of the reaction conditions, it was observed that the basicity of the reaction mixture required for the first step lowered the efficiency of the second step. Neutralization of reaction mixture *via* H_2SO_4 addition prior to the introduction of the hydrazine allowed to optimize this process.



4 **5**

R^1 = Ph, C_6H_4*p*-Cl, *i*-Pr
R^2 = H, Et, Bn
R^3 = H, Me, Ph, C_6H_4*p*-OMe, C_6H_4*p*-NO_2

Scheme 2

2.2. Condensation of α,β-unsaturated nitriles with hydrazines

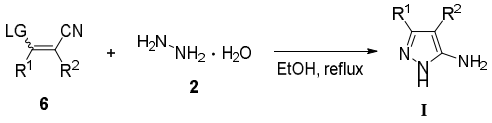
The second major route for 3-(5)-aminopyrazole synthesis is the condensation α,β-unsaturated nitriles with hydrazines. The formation of the aromatic heterocycle is secured by the presence of a leaving group on the alkene of the dielectrophilic partner.

2.2.1. With the hydrazine

Condensation of various α,β-unsaturated nitriles **6** bearing a leaving group at the β-position with the hydrazine hydrate **2** led uneventfully to the *N*-unsubstituted 3-(5)-aminopyrazoles **I** (Table 3). Various leaving group have been used such as ethoxy[15] (entry 1), dimethylamino[16,17] (entries 2 and 3), morpholino[18] (entry 4) and thiomethyl[19-21] (entries 5-7). Unsurprisingly, thiomethyl was found to be a better leaving group than amino group when both groups were present on the same substrate (entries 6 and 7). The reaction

conditions are compatible with a large number of functionalities allowing for example the synthesis of pyrazolo-nucleoside starting with an α,β-unsaturated nitriles bearing a ribosyl substituent at the α postion.[22]

Table 3



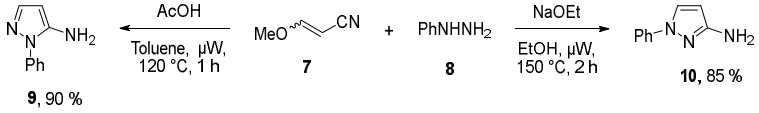
6 2 I

Entry	LG	R^1	R^2	Reaction time	Yield (%)	Ref
1	OEt	H	CN	30 min	86	15
2[a]	NMe_2	H	Pyridinyl	24 h	90	16
3	NMe_2	H	Ar	18 h	19-29 (2 examples)	17
4	Morpholinyl	$CH_2CH_2C_6H_4$*p*-Cl	CN	5 h	73	18
5	SMe	NH C_6H_4*p*-CF_3	CN	2.5 h	67	19
6[b]	SMe	ArNH	CN	24 h	84-98 (15 examples)	20
7	SMe	Morpholinyl, piperidinyl, pyrrolidinyl	CN	12 h	87-97	21

[a] AcOEt was used as solvent. [b] MeOH was used as solvent

2.2.2. With monosubstituted hydrazines

The use of monosubstituted hydrazine raises the problem of regioselectivity during the annelation process. Bagley *et al.* were able to develop regiodivergent conditions for the condensation of 3-methoxyacrylonitrile **7** and phenylhyrazine **8** (Scheme 3).[6] Under microwave activation, the use of AcOH in toluene led to the 5-aminopyrazole **9** (90% yield) whereas the use of EtONa in EtOH led to the 3-aminopyrazole **10** (85% yield). The same group confirmed this trend by using 3-bromophenylhydrazine that led to similar results.[23] The microwave activation was demonstrated to have no impact on the regioselective outcome of the reaction but to induce a tenfold reduction of reaction time.

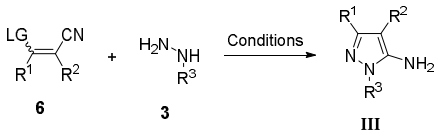


9, 90 % 7 8 **10**, 85 %

Scheme 3

Ashour and Leroux reported the regioselective synthesis of 5-aminopyrazoles **III** using hydrazines **3** and thiomethyl- or dimethylamino-substituted acrylonitriles **6** (Table 4).[24,25] The condensation of 2-[bis(methylthio)methylene]malononitrile and phenylhydrazine in methanol at reflux led to the desired 5-aminopyrazoles in 95% yield (entry 1).[24] Leroux *et al.* performed the synthesis of 3-(fluoroalkyl)-5-aminopyrazoles in quantitative yields from the corresponding difluoro(dimethylamino)ethylidenes in acetonitrile (entries 2 and 3).[25]

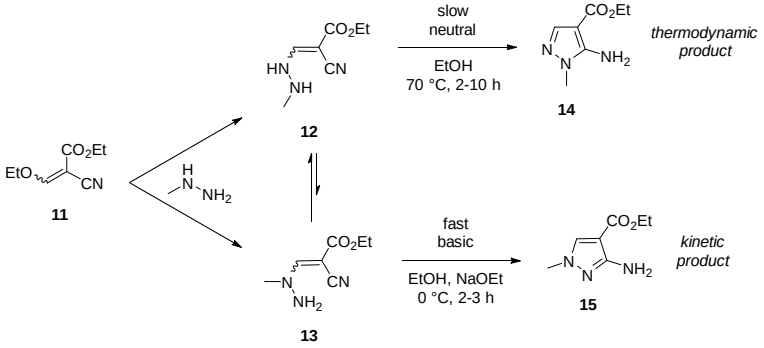
Table 4



6 3 III

Entry	LG	R^1	R^2	R^3	Conditions	Yield (%)	Ref
1	SMe	SMe	CN	Ph	MeOH, reflux, 3 h	96	24
2	NMe_2	CHF_2	CN	Me	MeCN, rt, 1 h	>99	24
3	NMe_2	CHF_2	CO_2Et	Me	MeCN, rt, 1 h	>99	25

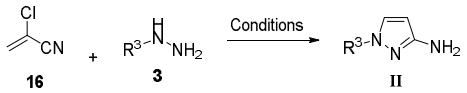
Fandrick *et al.* reported a detailed mechanistic study of the reaction between methyl hydrazine and ethyl 2-cyano-3-ethoxyacrylate **11** (Scheme 4).[26] Addition/elimination produced the Michael adducts **12** and **13**, the latter one being kinetically favored. A dynamic equilibration of the Michael adducts was demonstrated to favor **12**. Based on this dynamic equilibration, the authors were able to develop thermodynamic conditions (EtOH, 70 °C) leading to 5-aminopyrazole **14** and kinetic conditions (EtONa, EtOH, 0 °C) giving the 3-aminopyrazole **15**. This method was successfully extended to a wide variety of acrylonitriles and hydrazines.[26] An increase of the steric hinderance of hydrazine substituent was found to favor the 5-aminopyrazole regioisomer **14**.



Scheme 4

The use of acrylonitriles bearing a leaving group at the α-position such as 2-chloroacrylonitrile **16** has also been reported for the synthesis of 3-aminopyrazoles **II** (Table 5).[6,27] Bagley *et al.* reported the microwave-assisted condensation of **16** with methylhydrazine **3** to obtain exclusively and in high yield the 3-aminopyrazole regioisomer **II** (entry 1).[6] Ji studied the related condensation of *tert*-butylhydrazine hydrochloride and 2-chloroacrylonitrile.[27] The cyclization step appeared to be modulated by the ratio of additives and under optimal conditions, K_2CO_3:$NaHCO_3$ (1:2), the 3-aminopyrazole **II** was formed preferentially (entry 2).

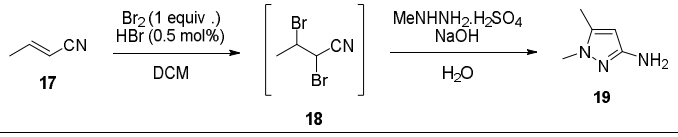
Table 5



Entry	R^3	Conditions	Yield (%)	Ref
1	Me	EtOH, μW, 100 °C, 6 min	81	6
2	*t*-Bu	H_2O, K_2CO_3:$NaHCO_3$ (1:2), rt, 18 h	50	27

A less classical strategy, based on a two-step procedure, has been reported by Eastgate (Table 6).[28]

Table 6



Entry	$MeNHNH_2.H_2SO_4$ (equiv.)	NaOH (equiv.)	Ratio 3/5-aminopyrazole	Yield over 2 steps (%)	Ref
1	1	3	>99:1	73	28
2	1.25	5.2	>77:23	72	29

Crotonitrile **17** was first submitted to bromination to produce **18**. The cyclization of this intermediate required a tedious optimization. Highly basic conditions (NaOH aq. 10 M, 3 equiv.) allowed to generate selectively the 3-aminopyrazole **19** (entry 1). The same group reported that under kilogram scale the selectivity was lowered even upon increased amount of base (entry 2).[29]

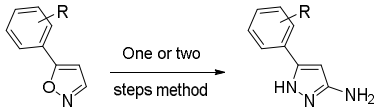
In 2009, Gong and Ryu applied this synthetic method using a solid-phase immobilized hydrazine. The condensation with cyanocarboimidates or substituted 3-ethoxyacrylonitriles under basic conditions gave the corresponding 3-aminopyrazole.[30]

2.3. Miscellaneous

The synthesis of 3-(5)-aminopyrazoles has also been reported using isoxazole and isothiazole as substrates instead of the classical linear 1,3-dielectrophiles.

2.3.1. Synthesis of aminopyrazoles from isoxazoles

Mitchell *et al.* studied the synthesis of 3-(5)-aminopyrazoles **21** from isoxazoles **20** according to a one step or two step procedure (Scheme 5).[31] In the one-step procedure the isoxazoles **20** are treated by hydrazine in DMSO at 90 °C. A ring-opening / ring-closing sequence allowed the formation of 3-(5)-aminopyrazoles **21** in good yields (74-92 %). In the two-step procedure, the isoxazoles **20** are first submitted to deprotonation leading to a β-ketonitrile intermediate. In a second step, the latter is submitted to the action of hydrazine to afford in good yields the 3-(5)-aminopyrazoles **21**. None of the two methods was found to be general and the differences of yields appeared difficult to rationalize in the absence of marked steric or electronic effects. Tube and flow NMR allowed to characterize five out of the nine intermediates of this transformation.



20 **21**

R = *p*-Cl, *p*-F, *p*-Me, *p*-OMe, *o*-OH, *m*-NO_2, *m*-CF_3

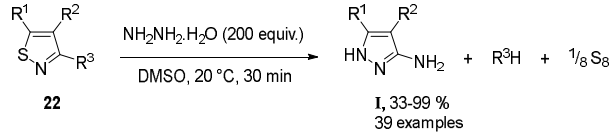
One step method: NH_2NH_2 (1.6 equiv.), DMSO, 90 °C, 15 h (74-92 %)

Two steps method: 1) KOH (1 equiv.), EtOH/H_2O, 50 °C, 30 min
2) NH_2NH_2 (1.4 equiv.), THF, AcOH, 60 °C, 2.5 h (59-93 %)

Scheme 5

2.3.2. Synthesis of aminopyrazoles from isothiazoles

Koutentis studied in 2009 the conversion of isothiazoles **22** to 3-(5)-aminopyrazoles using hydrazine (Scheme 6).[32] Addition of the hydrazine to the electrophilic R^1C carbon of **22** is followed by the opening of the ring through a R^1C-S cleavage. Elimination of R^3H and sulfur generates a nitrile functional group that is further trapped by the second nitrogen atom of the hydrazine to afford the aminopyrazole **I**.



22

I, 33-99 %
39 examples

R^1 = Ar, OR, NHR, SR, Cl; R^2 = CN, H, Br, Ph, NH_2; R^3 = Cl, Br, I, OMe, OH, NHR, Ph

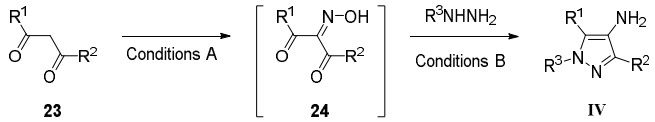
Scheme 6

3. Synthesis of 4-aminopyrazoles

3.1. Knorr pyrazole synthesis

The Knorr synthesis, based on the condensation of an hydrazine and a 1,3-dicarbonyl derivative **23**, was used to develop the access to several 4-aminopyrazoles **IV** (Table 7).[33-35] The reaction is based on a two-step procedure starting with the 1,3-dicarbonyl compound **23** that is converted to the oxime derivative **24** prior to the annelation step with hydrazine. The oxime is generally formed under acidic conditions using either HCl (entry 1) or AcOH (entries 2 and 3). The textbook mechanism of this reaction has been recently confirmed through *in situ* FT-IR, independent component analysis and DFT calculations.[36]

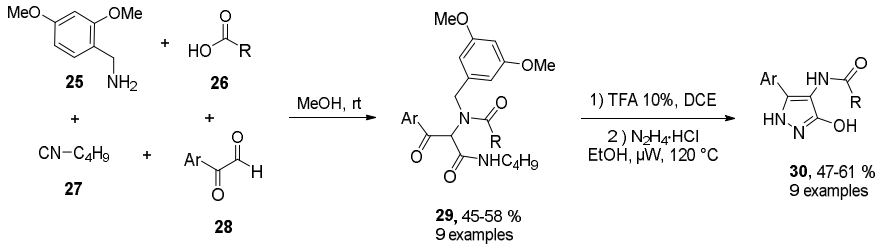
Table 7



23 **24** **IV**

Entry	R^1	R^2	R^3	Conditions A	Conditions B	Yield (%)	Ref
1	Ar	CO_2Me	Ar	$NaNO_2$, HCl, MeOH, rt	MeOH, rt	21-25 (4 examples)	33
2	Ph	CF_3	H	$NaNO_2$, AcOH, H_2O, rt	EtOH, rt	75 (1 example)	34
3	Me	Ph	H	$NaNO_2$, AcOH, H_2O, rt	EtOH, rt	57-78 (2 examples)	35

The Knorr pyrazole synthesis was also used to synthesize a library of 4-aminopyrazoles from Ugi adducts (Scheme 7).[37] The Ugi condensation of a primary amine **25** with a variety of carboxylic acids **26**, carbonyl compounds **28** and isocyanides **27** afforded the corresponding functionalized α-acylamino amides **29** in 45-58% yield. Acidic cleavage of the dimethoxybenzyl group followed by hydrazine condensation furnished nine 4-aminopyrazoles **30** in 47-61% yield over two steps.



25 **26** **27** **28**

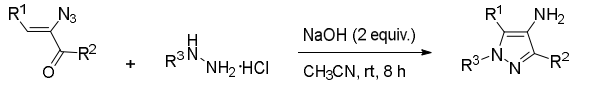
29, 45-58 %
9 examples

30, 47-61 %
9 examples

Scheme 7

3.2. Reaction of hydrazine with α,β-unsaturated ketones

The synthesis of a variety of tetra-substituted 4-aminopyrazoles **IV** has been recently developed by the condensation of hydrazines **3** and α,β-unsaturated ketones **31** bearing an azido group at the α position (Scheme 8).[38] The structure of the aminopyrazoles **IV** has been confirmed by X-ray crystal structure analysis.



31 **3**

IV, 45-92 %
15 examples

R^1 = Ar; R^2 = Ar, Het, Alk; R^3 = Me, Ph, Bn

Scheme 8

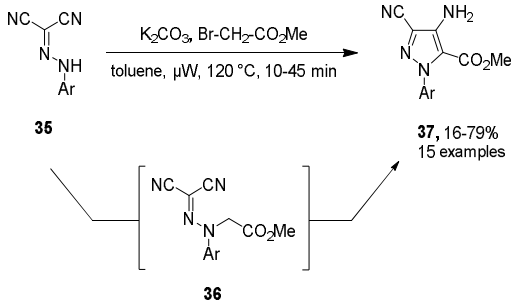
Interestingly, this publication also reported the replacement of the base NaOH with EtONa leading to an original and efficient access to 4-hydroxyprazoles instead of 4-aminopyrazoles.

The condensation of phenylhydrazine **32** and the enaminone **33**, easily accessible through a rhodium-catalyzed three components reaction, afforded selectively the 4-aminopyrazole **34** (Scheme 9).[39] The structure of **34** was confirmed by NOE analysis. It is interesting to note the opposite regioselectivity observed for the condensation of monosubstituted hydrazines with α,β-unsaturated ketones **31** (Scheme 8) or enaminone **33** (Scheme 9).

Scheme 9

3.3. Thorpe-Ziegler cyclization

Busca reported the synthesis of a library of tetrasubstituted 4-aminoyrazoles **37** *via* a Thorpe-Ziegler cyclization (Scheme 10).[40] The one-pot procedure is based on the alkylation of a variety of dicyanohydrazones **35** with methyl bromoacetate leading to the intermediates **36** followed by a ring-closure in basic conditions through a Thorpe-Ziegler reaction. Reaction conditions have been carefully optimized and the use of microwave activation in toluene allowed a spectacular 24-fold reduction of reaction time compared to classical thermal activation.



Scheme 10

4. Mono-functionalization of aminopyrazoles

Mono-functionalization of aminopyrazoles is based on reaction with electrophiles and there are numerous reports dealing with, for example, bromination,[41] Friedel-Craft type reactions[42] or aromatic nucleophilic substitutions.[43] We have decided to focus this bibliographical study on the emerging area of transition metal-catalyzed functionalization of aminopyrazoles which has not been reviewed before to the best of our knowledge.

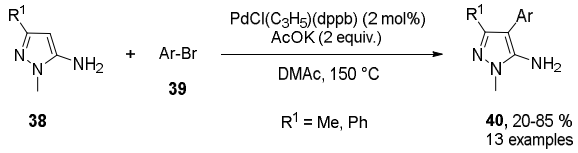
4.1. Transition-metal-catalyzed C-H functionalization of aminopyrazole

Although direct C-H functionalization is an ever-growing field of research, very few examples using aminopyrazoles as substrates were reported.

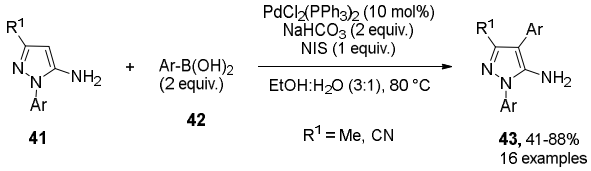
Doucet reported the palladium-catalyzed direct *C*-4 arylation of 5-aminopyrazoles **38** bearing a free primary amino group with aryl bromides **39** (Scheme 11).[44] The reaction, that is thought to proceed through a concerted metallation-deprotonation mechanism, led to compounds **40** in good yields with a variety of aryl bromides.

Under palladium catalysis, the use of boronic acids **42** in the presence of NIS allowed the direct *C*-4 arylation of 5-aminopyrazoles **41** (Scheme 12).[45] According to this strategy, derivatives **41** were converted to the desired compounds **43** in good yields. The authors suggest that NIS promoted the *in situ* formation of

4-iodo-aminopyrazoles that evolved next through a Suzuki-Miyaura cross-coupling reaction. Worthy of note, during the optimization of the reaction conditions, the use of $Cu(OAc)_2$ was found to be almost as efficient as $PdCl_2(PPh_3)_2$.

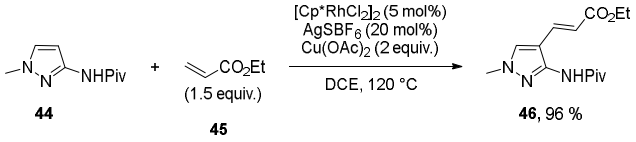


Scheme 11



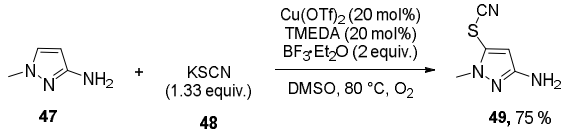
Scheme 12

Shi developed a rhodium-catalyzed Fujiwara-Moritani reaction with various pyridines and quinolones.[46] He also observed that *N*-1-methyl-3-aminopyrazole pivalamide **44** was a very reactive partner for this direct olefination reaction with ethyl acrylate **45** leading to the desired product **46** in an excellent 96% yield (Scheme 13). *N*-Pivalamide-directed *ortho* effect account for the complete *C*-4 selectivity.



Scheme 13

In 2017, Jiang and Wu reported a very elegant thiocyanation of (hetero)aromatics based on a direct C-H functionalization.[47] This method is in line with the development of sustainable chemistry, using copper as catalyst and O_2 as oxidant. Experimental investigations led the authors to propose a mechanism based on a C-H activation followed by a Cu(II)/Cu(III) catalytic cycle. The *N*-methyl-3-aminopyrazole **47**, bearing a free primary amino group, was found to be a good substrate for this transformation. On the use of potassium thiocyanate **48**, the thiocyanato-aminopyrazole **49** was afforded in 75% yield (Scheme 14). Related thiocyanation of aminopyrazoles has also been reported by anodic oxidation of NH_4SCN through electroinduced nucleophilic aromatic substitution.[48]



Scheme 14

4.2. Transition-metal-catalyzed *N*-arylation of aminopyrazoles

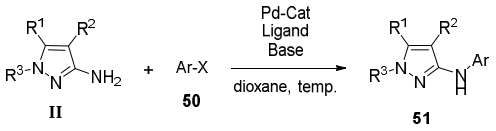
During this decade there has been a tremendous development of palladium-catalyzed *N*-arylations of (hetero)aromatic substrates. The efficiency of this method to generate large libraries of compounds for medicinal chemistry has led to its application to aminopyrazoles. Considering the *N-endo*/*exo* selectivity for arylation processes, two types of substrates can be distinguished. On one hand, unbiased aminopyrazoles in

which all of the nitrogen atoms are potential partners and, on the other hand, biased aminopyrazoles in which the chemoselectivity is dictated by the substrate structure.

4.2.1. Palladium-catalyzed *N*-arylation with biased aminopyrazoles

Palladium-catalyzed arylation of biased 3-aminopyrazoles **II** with aryl halides **50** has been reported by only two groups (Table 8).[49,50] In both reports, aminopyrazoles were substituted at the *N*-1 position by an alkyl group while the primary amino group was unprotected. The use of the couple $Pd_2(dba)_3$/Xantphos as a catalyst in dioxane allowed the arylation in good yields to give 3-aminopyrazoles **51** using either an organic base (entry 1) or an inorganic one (entry 2).

Table 8

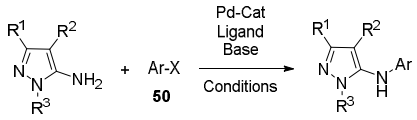


II 50 51

Entry	R^1	R^2	R^3	Ar	X	Pd-cat / ligand	Base	Temp. (°C)	Yield (%)	Ref
1	Alkyl	H	Alkyl	Pyridinyl	Br	$Pd_2(dba)_3$ / Xantphos	*t*-BuONa	80	7-66	49
2	H	H	Me	Pyridminyl	Cl	$Pd_2(dba)_3$ / Xantphos	Cs_2CO_3	140	43-87	50

Free primary amino group of 5-aminopyrazoles **III** were found to be good partners for Buchwald-Hartwig arylation reactions with aryl halides **50** (Table 9).[51-56] In almost all cases, inorganic bases and protic solvents were found efficient to promote the coupling leading to 5-aminopyrazoles **52** (entries 1-5) although Buchwald successfully reported the alternative use of LiHMDS in toluene (entry 6).

Table 9



III 50 52

Entry	R^1	R^2	R^3	Ar	X	Pd-cat/Ligand	Base	Conditions	Yield (%)	Ref
1	Me	H	Me	Aryl	Cl	BrettPhos precatalyst/ RuPhos	Cs_2CO_3	*t*-BuOH, 80 °C	97	51
2	Me	H	PMB	Imidazo-pyridizinyl	Cl	$Pd_2(dba)_3$/ Xantphos	NaOH	Toluene/ water	79	52
3	Me	H	Boc	Pyrimidinyl	Cl	$Pd(OAc)_2$/ Xantphos	Cs_2CO_3	Dioxane, rt	62-81	53
4	H	H	Me	Pyrimidinyl	Cl	*t*-BuBrettPhos precatalyst/ -	Cs_2CO_3	*t*-BuOH, 80 °C	77	54
5	H	Pyridyl	Alkyl	Aryl	Br	$Pd_2(dba)_3$/ BINAP	Cs_2CO_3	PhMe/*t*-BuOH 110 °C	60-70	54
6	H	H	HetAr	Indazoyl	Br	*t*-BuBrettPhos precatalyst/ *t*-BuBrettPhos	LiHMDS	THF, 65 °C	69	56

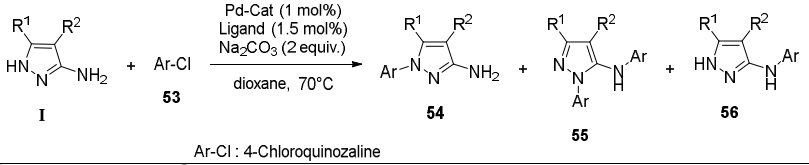
4.2.2. Palladium-catalyzed *N*-arylation with unbiased aminopyrazoles

The use of unbiased aminopyrazoles in Buchwald-Hartwig *N*-arylation reactions has been the subject of limited number of reports.

Chen and Hu reported an interesting study that demonstrated the importance of steric effects for the selectivity of palladium-catalyzed *N*-arylation (Table 10).[57] Treatment of 3-aminopyrazoles **I** with 4-

chloroquinozaline **53** under palladium catalysis led to a 73 % yield of the *N*-1 arylated 3-aminopyrazole **54** (entry 1). Adding steric hindrance around *N*-1 led to a complete inversion of the selectivity in favor of the *N*-2 substituted aminopyrazoles **55** (entries 2 and 3). Moreover, in the absence of a palladium catalyst, the authors observed the formation of the *N*-3-arylated product **56** through a classical S_NAr reaction (entry 4). They also noticed that the *endo*/*exo N*-selectivity is highly dependent on the reaction conditions. Indeed, ligands such as dppf, dppb and BINAP were found to favor the formation of the *N*-3-arylated product. A similar trend was observed when NaOAc was used as a base.

Table 10

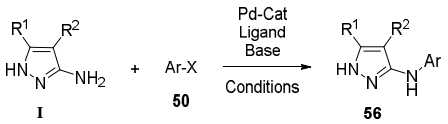


Ar-Cl : 4-Chloroquinozaline

Entry	R^1	R^2	Pd-Cat	Ligand	Product	Yield (%)
1	H	H	$Pd_2(dba)_3$	Xantphos	**54**	73
2	Me	H	$Pd_2(dba)_3$	Xantphos	**55**	73
3	CH_2CO_2Et	H	$Pd_2(dba)_3$	Xantphos	**55**	62
4	Me	H	-	-	**56**	99

However, three independent contributions reported the selective access to **56** on the use of unbiased aminopyrazoles **I** through palladium-catalyzed coupling reactions with aryl halides **50** (Table 11).[58-60] Interestingly, in all those examples hindered electron rich ligands were used as ligand and *t*-BuOH was found to be the solvent of choice using either organic (entry 1) or inorganic (entries 2 and 3) bases leading to the *N*-3 arylated derivatives **56** in moderate to excellent yields.

Table 11

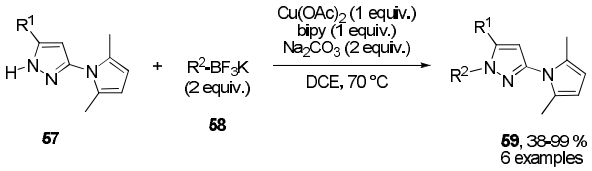


Entry	R^1	R^2	Ar	X	Pd-Cat/Ligand	Base	Conditions	Yield (%)	Ref
1	Me	H	Ph, HetAr	Br	*t*-BuXphos precatalyst/ *t*-BuXphos	*t*-BuONa	*t*-BuOH, rt	48-96	58
2	H	H	HetAr	Cl	$Pd_2(dba)_3$/ CyPF-*t*-Bu	Cs_2CO_3	*t*-BuOH/H_2O, 90 °C	39-50	59
3	Me, *i*-Pr	H	Ar, HetAr	Cl, Br	$Pd_2(dba)_3$/ *t*-BuBrettPhos	K_3PO_4	*t*-BuOH	84-92	60

4.2.3. Copper-catalyzed *N*-arylation with biased aminopyrazoles

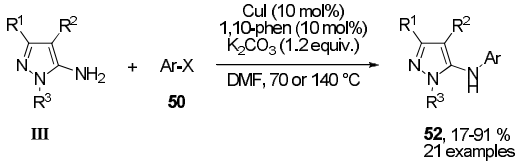
A complete regioselective *N*-1 functionalization of *N*-3 protected aminopyrazole **57** with potassium trifluoroborate substrates **58** was observed under stoichiometric Chan-Lam conditions (Scheme 15).[27] Worthy of note, the authors observed that, as opposed to potassium trifluoroborates, the use of boronic acids derivatives did not allow the formation of the desired coupling products **59**.

On the other hand, the *N*-5 arylation of *N*-1 substituted 5-aminopyrazoles **III** has been developed using Ullmann conditions (Scheme 16).[61] The use of copper iodide and 1,10-phenantroline in the presence of K_2CO_3 efficiently promoted the coupling with aryl halides **50** to allow the access to compounds **52**. Ullman conditions have also been reported to successfully allow the *N*-1 arylation of aminopyrazoles bearing a *N*-3 acetamido group.[62]



R^1= H, Me, *i*-Pr, cyclopropyl
R^2= vinyl, cyclopropyl, isopropenyl

Scheme 15

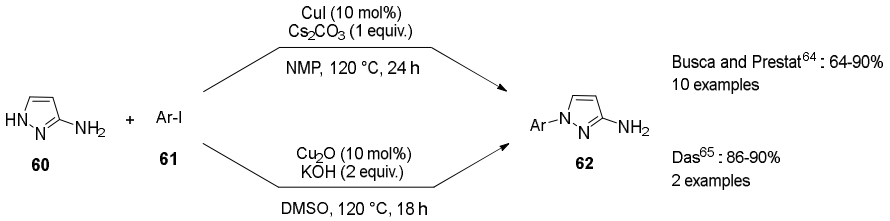


R^1= aryl, pyridyl, quinolinyl
R^2= H
R^3= *t*-Bu, Ph, C_6H_4*p*-Cl, C_6H_4*p*-Me, C_6H_4*p*-OMe
Ar=Ph, Tol, C_6H_4*p*-OMe
X= I, Br, Cl

Scheme 16

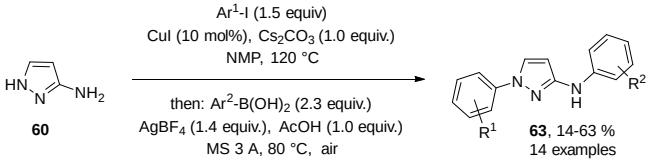
4.2.4. Copper-catalyzed *N*-arylation with unbiased aminopyrazoles

Seminal work from Buchwald group established that for Ullmann arylation the use of unbiased aminopyrazoles resulted to the arylation of the endocyclic nitrogen atoms.[63] This result has been confirmed in 2015 by Busca and Prestat, and in 2016 by Das (Scheme 17).[64,65] Indeed, the arylation of 3-aminopyrazoles **60** with various aryl iodides **61** under copper(I) catalysis was found to afford in high yield and high chemo and regioselectivity the *N*-1 arylated 3-aminopyrazoles **62**.



Scheme 17

Taking advantage of the selectivity of Ullman coupling for endocyclic nitrogen atoms, Busca and Prestat developed a one-pot *N*-1,*N*-3-diarylation of 3-aminopyrazole **60** based on Ullman/Chan–Lam sequence (Scheme 18).[64] They were able to develop reaction conditions allowing two successive Cu(I)/Cu(II)-catalyzed C-N bond-formation events performed by a unique copper source leading to the *N*-1, *N*-3 diarylated 3-aminopyrazoles **63**.

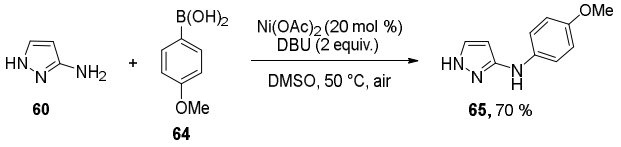


Scheme 18

Such an assisted tandem catalysis is triggered by a change in the oxidation state of the metal. Of note, Busca and Prestat reported a total absence of selectivity on the use of Chan-Lam coupling conditions with unbiased 3-aminopyrazole while Das reported two selective examples of *N*-1 arylations.[64,66]

4.2.5. Nickel-catalyzed *N*-arylation with unbiased aminopyrazoles

Nickel-catalyzed variant of the Chan-Lam coupling has been recently developed.[67] This methodology was reported to selectively promote the arylation of the *exo* nitrogen atom of aminopyrazole **60**, upon reaction with boronic acid **64**, to afford the arylated products **65** in good yield (Scheme 19).[65]



Scheme 19

4.3. Conclusion

Unsurprisingly most of the reported transition-metal-catalyzed mono-functionalization of aminopyrazoles is based on Buchwald-Hartwig *N*-arylations. Chemoselective *N*-arylation of the primary amino group is classically observed although the use of biased substrates or specific reaction conditions were reported to allow the arylation of one *endo* nitrogen atom. Interestingly, the copper-catalyzed Ullmann *N*-arylation leads to the selective *N*-arylation of the *endo* nitrogen atoms and is thus complementary of palladium catalysis. Copper-catalyzed Chan-Lam reactions allow the arylation of both *exo* and *endo* nitrogen atoms without selectivity. Direct transition-metal-catalyzed C-H functionalization has been scarcely studied and those studies were almost exclusively dedicated to Csp^2-Csp^2 forming-bond reactions. The C-H *ortho* to the primary amino group is favored for those functionalizations. Selective mono-functionalization processes based on transition-metal-catalysis reported so far are summarized in the following figure (Figure 1).

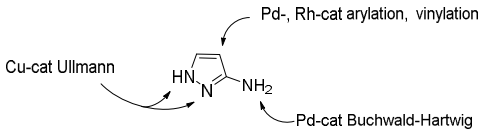


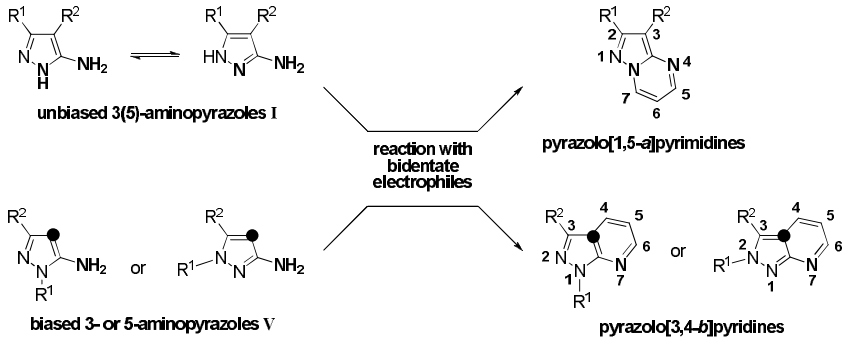
Figure 1

5. Di-functionalization of aminopyrazoles

5.1. General trends of chemical reactivity

The use of aminopyrazoles as versatile building blocks that allow an efficient access to molecular diversity is well exemplified by the work of Al-Etaibi's group[68] and that of Busca *et al*.[40] Aminopyrazoles embed three to four potential nucleophilic sites which can indeed react with numerous dielectrophilic species. Chemoselectivity is generally dictated by the structure of aminopyrazoles and will be detailed in separate sections: unbiased 3-(5)-aminopyrazoles **I** (R=H) usually react as 1,3-diamine species to afford pyrazolo[1,5-*a*]pyrimidines while biased 3- or 5-aminopyrazoles **V** (R≠H) generally behave as enamine-type nucleophiles to yield pyrazolo[3,4-*b*]pyridines (Scheme 20). Over the last decade, the chemistry of 5-aminopyrazoles was at full growth whereas very few reports were dealing with the reactivity of biased 3-aminopyrazoles. For the sake of clarity, these scarce examples will not be represented in the schemes but will be mentioned below.

Beyond chemoselectivity, the use of unsymmetrical dielectrophilic reagents can lead to regiochemistry issues. Whenever this is the case, emphasis will be made on analytical methods such as 2D NMR experiments or XR analysis that were used by the authors to unambiguously assign the structures of regioisomers.



Scheme 20

Worthy of note, the synthesis of pyri(mi)dinone will not be reviewed, neither will be reactions relying on *C*-3/*C*-4 specific substitution patterns.

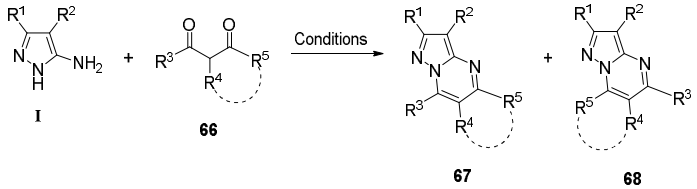
5.2. Formation of pyrazolo[1,5-*a*]pyrimidines

Unbiased aminopyrazoles **I** (R^1=H) react preferentially with bidentate electrophilic reagents such as ketone or Michael acceptors *via* their *N*-1 and *N*-5 nucleophilic sites and thus provide an efficient one-step and chemoselective access to pyrazolo[1,5-*a*]pyrimidines. If the difunctional reagent is unsymmetrical, regioselectivity is dictated by the greater nucleophilicity of *N*-5 *vs N*-1.

5.2.1. Reaction with β-diketones

Condensation of aminopyrazoles **I** with β-diketones **66** can afford mono-, di- or tri-substituted pyrimidines (Table 12).[69-75] This reaction usually leads to a mixture of regioisomers **67** and **68**, unless the reagent is symmetrical (R^3=R^5). The use of cyclic β-diketones (dot lines) **66**, allows the access to linear **67** or angular **68** tricyclic products.

Table 12



Entry	R^1	R^2	R^3/R^5	R^4	Conditions	Product, Yield (%)	Ref
1	H, Me, OAlk, SAlk, NHAlk, $NAlk_2$, 1-Boc-piperazinyl	SO_2Ar	H, OH, Alk Cyclopentyl, cyclohexyl	H, Cl, Alk NHCOMe	AcOH, ± HCl, rt, 100 °C, 6-12 h	**67+68**, 20-85 (57 examples)	69-73
2	Me, NH_2	N=N-C_6H_4*p*-OH	Me	H	AcONa, AcOH, reflux, 1 h	**67** = **68**, 72-77 (2 examples)	68
3	C_6H_4*p*-OMe	CH_2-CO_2*t*-Bu	Et	H	EtOH, µW, 185 °C, 80 min	**67** = **68**, 80	74
4	C_6H_4*p*-$(CH_2)_3F$	CH_2CO_2Et	Me	H	EtOH, reflux, 5 h	**67** = **68**, 86	75

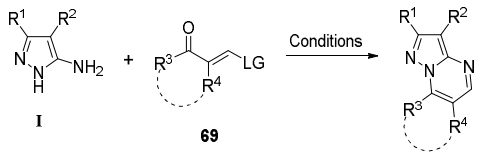
Over the last decade, the team of Okun employed this strategy several times to develop serotonin 5-HT6 receptor antagonists by using linear reagents, either unsubstituted[69,70] (R^4=H) or substituted[71] (R^4≠H), but also cyclic ones such as formyl and acetyl-cycloacanones[72,73] under acidic conditions (entry 1). In most of the cases, no regiocontrol was observed and the authors systematically separated isomers **67** and **68** to pursue the synthesis and test both series of final compounds. The only reported exception was for cyclopentanones which yielded predominantly angular tricyclic structures **68**. Structures of **67** and **68** were unambiguously assigned with 2D NMR experiments (NOESY+HMBC) and some of them were confirmed with X-ray crystallography. Worthy of note, this reaction tolerates phenol and azo groups (entry 2).[68] Moreover, in presence of acid-labile functions, the condensation can be performed in ethanol under neutral conditions with (entry 3)[74] or without (entry 4)[75] microwave activation.

When β-diketo compounds are replaced by β-keto esters or diesters, the reaction yield the corresponding pyridinones but this aspect will not be covered here.[76]

5.2.2. Reaction with activated enones

Reaction of aminopyrazoles **I** with enaminones (LG=NR_2) or their ethoxy surrogates **69** (LG=OEt) allows the regioselective synthesis of mono- or di-substituted pyrimidines **70** (Table 13). Sadek and Moustafa studied the mechanism and revealed that it proceeds by initial 1,4-attack of the exocyclic amine before the subsequent ring closure by condensation of the intracyclic nitrogen with the carbonyl.[77] This mechanism accounts for the observed selectivity. When Kim *et al.* compared the reactivity of arylacetoaldehydes *vs* the corresponding β-enaminoketones, the latter appeared to yield predominantly the pyrimidine **70** whereas the former led to a regioisomeric mixture (entry 1).[78] The structure of **70** was unambiguously confirmed by X-ray crystallographic analysis. This regioselectivity was also supported by the results disclosed by Al-Eitaibi (entry 2).[68] Acidic conditions are not mandatory as demonstrated by the team of Al-Matar who performed the synthesis of benzoylated pyrazolo-pyridines **70** under neutral conditions (entry 3).[79] Condensation of sophisticated TMS-protected enyones was also successfully achieved under neutral conditions and allowed the introduction of an alkyne moiety as substituent R^3 (entry 4).[80] Worth noting are the retention of the TMS group in all products and the absence of Michael-type adducts to the triple bond. X-ray analysis data were collected to unambiguously prove the structures.

Table 13



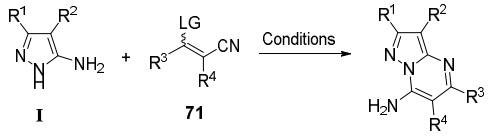
Entry	R^1	R^2	R^3	R^4	LG	Conditions	Yield (%)	Ref
1	Ar	H	Ar	H	NMe_2	AcOH, rt, 12 h	60-90 (16 examples)	78
2	NH_2, Me	N=N-C_6H_4*p*-OH	Ar, HetAr	H	NMe_2	AcONa, AcOH, reflux, 1 h	72-85 (10 examples)	68
3	COAr	H	Ph	H	NMe_2	EtOH, reflux, 8 h	60-65 (2 examples)	79
4	H, Me, Ar, CH_2CN	H, CN, CO_2Et, Ph	C≡C-TMS	Ar	OEt	EtOH, 80 °C	61-94 (32 examples)	80
5	CO_2Me	H		CO_2Me	NMe_2	MeOH, rt	10-32 (2 examples)	81
6	Me, NH_2, Ph, OH	H, CO_2Et, Ph, N=N-Ph	Cycloalcanone		NMe_2	DMF, µW, 150 °C, 15 min	82-89 (7 examples)	77

With chiral enaminones prepared from α-amino-acids, the reaction was performed at room temperature to avoid epimerisation of the stereogenic center but without heating the reaction is less efficient (entry 5).[81] Interestingly, the enaminone can be synthesized *in situ* through a MCR process by mixing a β-diketone and DMF-DMA under microwave activation (entry 6).[77]

5.2.3. Reaction with acrylonitriles

Addition of aminopyrazoles **I** on acrylonitriles **71** such as enaminonitriles (LG=NR_2) or benzylidenemalononitrile (LG=H) enabled the formation of 7-amino-pyrazolo[1,5-*a*]pyrimidines **72** (Table 14). Reassignment of these structures was achieved by Al-Mousawi *et al.* based on the results of ^{15}N HMBC and X-ray crystallographic analyses which excluded the isomeric adduct bearing the amino group in *ortho* position.[82] This is consistent with a mechanism initiated by a Michael addition of *N*-4 followed by ring closure between *N*-1 and the nitrile function. On the use of enaminonitriles, the reaction leads to unsubstituted aminopyrimidines **72** (R^3=R^4=H). When a primary amine is used as leaving group the yields are very low (entry 1)[71] whereas a piperidinyl moiety allows the reaction to reach 70-75 % yield (entry 2).[68] When the pyrazole bears labile groups such as a thiazole ring, the acidic catalysis can be skipped without any drop of the yield (entry 3).[82] When benzylidenemalononitriles are employed, the mechanism is slightly different and requires an oxidative aromatization step. Acidic (entry 4)[68] or neutral conditions (entry 5)[82] seems to be equally efficient to provide polysubstituted aminopyrimidines **72** (R^3=Ph, R^4=CN).

Table 14



I **71** **72**

Entry	R^1	R^2	R^3	R^4	LG	Conditions	Yield (%)	Ref
1	NHMe	SO_2Ar	H	H	NH_2	AcOH, 100 °C, 15 h	22-35 (2 examples)	71
2	Me, NH_2	N=N-C_6H_4*p*-OH	H	H	Piperidinyl	AcONa, AcOH, reflux, 1 h	70-75 (2 examples)	68
3	NH_2	Thiazolyl	H	H	Piperidinyl	DMF, reflux, 10 h	70	82
4	Me, NH_2	N=N-C_6H_4*p*-OH	Ph	CN	H	AcONa, AcOH, reflux, 1 h	60-63 (2 examples)	68
5	NH_2	Thiazolyl	Ph	CN	H	DMF, reflux, 10 h	75	82

Surprisingly, there is no report during this decade of a MCR version using benzaldehyde and malononitrile to generate *in situ* the Michael acceptor.

5.2.4. Miscellaneous

Few other methodologies were developed to provide a one-step access to pyrazolo[1,5-*a*]pyrimidines from amino-pyrazoles. These procedures include MCR with arylaldehydes and alkynes[83] or ketones,[84] as well as condensation with α-carbonyl-allenes[85] or 1,5-diketones.[86]

5.3. Formation of pyrazolo[3,4-*b*]pyridines

Biased aminopyrazoles **V** (R^1≠H) react with bidentate electrophilic reagents such as ketone or Michael acceptors *via* their *C*-4 and *N*-5 nucleophilic sites and thus provide an efficient one-step access to pyrazolo[3,4-*b*]pyridines.

If the difunctional reagent is unsymmetrical, regioselectivity is usually dictated by the greater nucleophilicity of *C*-4 over *N*-5, corresponding to an enamine reactivity. However, few authors are assuming

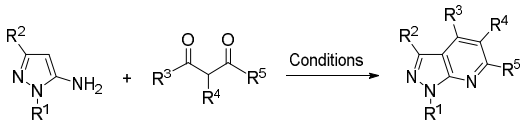
that aminopyrazoles can also react as simple aromatic amines. These considerations will be discussed in the following section.

Interestingly, two chemoselective methods were reported to afford 1*H*-pyrazolo[3,4-*b*]pyridines from unbiased aminopyrazoles **I** (R^1=H) that are substrates usually leading to a pyrazolo[1,5-*a*]pyrimidines (see section 5.2). For the sake of clarity, these examples will also be described below.

5.3.1. Reaction with β-diketones

Condensation of aminopyrazoles **V** with β-diketones **73** under acidic conditions can afford mono-, di- or tri-substituted pyridines **74** (Table 15).[87-90] A plausible mechanism involves a Combes-type heterocyclization, *ie* initial formation of an iminium followed by the nucleophilic attack of the corresponding tautomeric enamine. If the β-diketones is not symmetrical, the substituent found as R^3 should be thus the most EWG. According to this strategy, a library of 17 pyridines **74** bearing an ester function as R^5 substituent was generated with the use of ethyl-2,4-dioxo-4-phenylbutanoates (entry 1).[87] Structures were confirmed by ^{1}H and ^{13}C NMR spectroscopies. Surprisingly, contradictory results were reported by Volochnyuk *et al.*who, obtained pyridines **74** with the ester function as R^3 substituent (entry 2).[88] Similar results were disclosed for CF_2-containing dielectrophiles that afforded pyridines **74** with the fluorinated EWG as R^5 substituent (entry 3).[89] Few years later, Iaroshenko described the use of *in situ*-generated silyl-enolate of nitro-malonaldehyde to furnish nitro-pyrazolopyridines **74** (entry 4).[90] The authors suggested a mechanism where the aminopyrazole acts not as an aromatic amine but as an enamine to attack the electrophile *via* the *C*-4 position. This could explain the different regioselectivities presented in Table 15.

Table 15



V **73** **74**

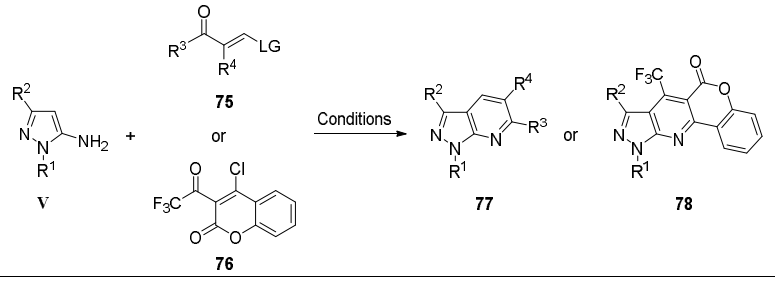
Entry	R^1	R^2	R^3	R^4	R^5	Conditions	Yield (%)	Ref
1	Ph	Me, Ph	Ar	H	CO_2Et	AcOH, reflux, 5 h	60-90 (17 examples)	87
2	Alk, Ar, HetAr	H, Me	CO_2Me, CO_2Et	H	Alk, Ar, HetAr	AcOH, reflux, 2-4 h	90 on average (58 examples)	88
3	Ph	Me	CF_2H, CF_2Cl, CF_2All	H	Me, Ar	AcOH, reflux, 6 h	60-87 (7 examples)	89
4	Ph	Me	H	NO_2	H	TMSCl, DMF, 100 °C, 2-12 h	88	90

Over the last decade, there is only one report of such a reaction performed with 3-aminopyrazole.[91]

5.3.2. Reaction with activated enone

As described in a previous section, activated enone **75** can dictate the regiochemistry and their condensation with biaised aminopyrazoles **V** was reported to result exclusively in 5,6-disubstituted pyridines 7**7** as single regioisomer (Table 16).[92-94] The 4-chloro-3-(trifluoroacetyl)-coumarin **76** appeared also to be a suitable reagent to afford tricyclic chromeno[4,3-*d*]pyrrolo[2,3-*b*]pyridines **78**. This strategy was used by Bayer to develop soluble guanylate cyclase stimulator Vericiguat (BAY 1021189) for the treatment of chronic heart failure under protic acid catalysis (entry 1).[92] Activation of the enaminone can also be achieved with Lewis acid such as TMSCl (entry 2).[93] In these both cases, the only way to explain this chemoselectivity is to consider that the aminopyrazole reacts as an enamine. In the case of 4-chloro-coumarin, the surprising regiochemistry pattern forced the authors to confirm the structure by ^{1}H, ^{13}C and ^{19}F NMR analysis (entry 3).[94] They concluded that, due to the high degree of aromaticity of the ring, the exocyclic NH_2 behave like an aromatic amine and not as an enamine.

Table 16



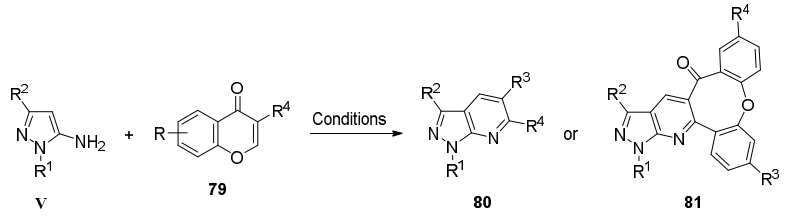
V **75** **76** **77** **78**

Entry	R^1	R^2	R^3	R^4	LG	Conditions	Product, Yield (%)	Ref
1	C_6H_4*o*-F	CO_2Et	H	F	Morpholinyl	MsOH, LiCl, EtOH, reflux, 4.5 h	**77**, 81	92
2	Ph	Me	Ar, HetAr	H	NMe_2	TMSCl, DMF, 90-120 °C, 1-2 h	**77**, 65-78 (4 examples)	93
3	Ph	Me	Fused coumarin		Cl	TMSCl, DMF, 100-120 °C, 2-12 h	**78**, 51	94

5.3.3. Reaction with chromones

The reactivity of various chromones **79** towards 5-aminopyrazoles **V**, leading to simple 6-arylated pyridines **80** or more complex polycyclic systems **81**, has been widely studied by the team of Langer and Iaroshenko (Table 17).[93,95-100] The mechanism is believed to start by a Michael-type 1,4-nucleophilic addition of the enamine that leads to pyrone ring-opening followed by intramolecular heterocyclization through amine and carbonyl condensation. Chromones appeared to be as efficient as enaminones to afford fused pyridines **80** bearing an *o*-OH-aromatic moiety as R^4 substituent with 84 % yield *vs* 82 % (entry 1).[93] In the case of the 5-nitro derivative (entry 2),[95] the structure was confirmed by X-ray crystal structure analysis. When the 3-methoxallylchromone was used, the enhanced electrophilicity of the 1,2-diketo system led to another regioisomer bearing the aromatic ring as R^3 substituent (entry 3).[96]

Table 17



V **79** **80** **81**

Entry	R^1	R^2	R^3	R^4	Conditions	Product, Yield (%)	Ref
1	Ph	Me	H	Naphtyl*o*-OH	TMSCl, DMF, 90-120 °C, 1 h	**80**, 84	93
2	Ph	Me	NO_2	C_6H_4*o*-OH	AcOH, reflux, 1 h	**80**, 97	95
3	Ph	Me	COC_6H_4*o*-OH	CO_2Me	AcOH, reflux, 2 h	**80**, 73	96
4	Me, Ph	Me	H, F	H, Cl	K_2CO_3, DMF, 120 °C, 16 h	**81**, 40-60 (2 examples)	99
5	H	H, Me, OH, Ar, HetAr	Ar*o*-NH_2, HetAr*o*-NH_2	H	$AlCl_3$, MeOH, reflux, 3-5 h	**80**, 43-83 (25 examples)	100

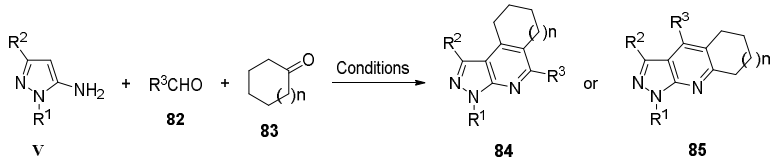
Worthy of note, 3-trifluoroacetyl-[97] and 3-dichloroacetyl-chromones[98] failed to yield the expected pyridines **80** while *o*-fluoro-3-benzoylchromones lead to complex tetracyclic compounds **81**, *via* a subsequent intramolecular cyclisation (entry 4).[99] Interestingly, indole-3-carboxaldehyde derivatives appeared to react similarly and furnished the corresponding pyridines **80** bearing *o*-NH_2-Ar moieties as R^3 substituents as confirmed by X-ray crystallography (entry 5).[100] These reaction conditions are the only ones to favour the formation of 1*H*-pyrazolo[3,4-*b*]pyridines while unbiased aminopyrazoles (R^1=H) are usually leading to a pyrazolo[1,5-*a*]pyrimidines. However, according to TLC analysis, the postulated mechanism proposed by the authors does not involve the aminopyrazole as an enamine but as an aromatic amine that forms first an imine. The same year, 3-acylindoles were also used by Langer and Iaroshenko who observed the same regioselectivity.[101]

5.3.4. MCR with aldehyde and ketone

Three-component reaction of biased aminopyrazoles **V** with aromatic aldehydes **82** and cyclic ketones **83** is an efficient synthetic strategy for the construction of macrocyclane-fused pyrazolo-pyridines **84** or **85** (Table 18).[102-104] This MCR can lead to regioisomers, **84** under acidic conditions or **85** under basic conditions. All the reports agree on the same putative mechanism accounting for structure **84** that relies upon condensation of the aminopyrazole **V** with the aldehyde **82**, affording an aromatic imine intermediate that undergoes Povarov-like cycloaddition with the enol derived from the ketone **83**.

The team of Jiang and Tu was the first in 2011 to report the synthesis of a 44 pyridines **84** library using acidic conditions under microwave irradiation (entry 1).[102] They pursued their studies with cyclopentanone, cyclohexanone and tetrahydrothiopyran-4-one (entry 2).[103] Acidic conditions appeared to be necessary to afford pyrazolopyridines **84**, while basic conditions lead to isomers **85**. Both structures were unequivocally determined by X-ray diffraction. For the latter, the authors proposed a mechanism based on Knoevenagel-type condensation between the aldehyde **82** and the ketone **83** followed by intermolecular Michael addition of the enamine as key steps. This work was later replicated in water by Zhang *et al.* to test the efficiency of a carbonaceous material (C-SO_3H) as solid acid catalyst (entry 3).[104]

Table 18



V **84** **85**

Entry	R^1	R^2	R^3	Cyclic ketone	Conditions	Product, Yield (%)	Ref
1	Ph	Me	Ar, HetAr	Cycloheptanone, cyclooctanone, cyclododecanone	TFA (1 equiv.), AcOH, 140 °C, µW, 15 min	**84**, 70-88 (44 examples)	102
2	Ph	Me	Ar, HetAr	Cyclopentanone, cyclohexanone, tetrahydrothiopyran-4-one	AcOH, 120 °C, µW, 15-20 min NaOH, DMF, 120 °C, µW, 15-20 min	**84**, 78-90 (33 examples) **85**, 75-87 (11 examples)	103
3	Ph	Me	Ar, HetAr	Cyclopentanone, cyclohexanone, cycloheptanone	C-SO_3H (10 mg), H_2O, 60 °C, 6 h	**84**, 67-86 (21 examples)	104

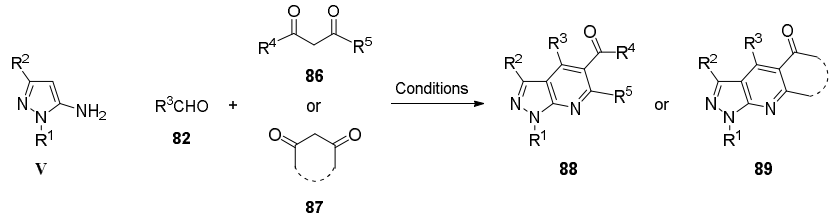
Over the last decade, only one example of acid-catalyzed MCR was reported starting from 3-amino-pyrazole.[6]

5.3.5. MCR with aldehyde and dicarbonyl reagent

When aminopyrazoles **V** react with a non-enolisable aldehyde **82** and 1,3-diketones **86** or **87**, the resulting 3-MCR can afford a pyrazolo[3,4-*b*]pyrimidine **88** or **89** bearing a ketone, an ester or an amide function in position 5 (Table 19).[105-108] A plausible mechanism is based on a Knoevenagel-type condensation yielding an α,β-unsaturated dicarbonyl intermediate that subsequently undergoes a Michael addition of the enamine function before a final cyclization/aromatization process.

With linear diketo reagents **86**, the team of Perumal reported the synthesis of trisubstituted pyridines **88** catalyzed by L-Proline (entry 1).[105] The regiochemistry observed throughout this library, with the CF_3 found as R^5 substituent and the carbonyl in position 5, was confirmed by X-ray crystallographic study. Of note, L-proline is an efficient catalyst whilst either pyrrolidine or formic/acetic acid failed to catalyse this reaction. A 4-MCR version of this reaction was described by Shaabani *et al*, that involves a diketene and an amine as starting material in order to generate *in situ* the dicarbonyl species, and afford a carboxamide in position 5 (entry 2).[106] Using cyclic diketo reagents **87**, Kar and Yadav described the synthesis of tricyclic pyrazolopyridines **89** (entry 3).[107] In few cases, the reaction stopped at the dihydropyridine intermediate, and as no aromatization occurred even after a prolonged reaction time, the authors added DDQ in acetonitrile to yield the aromatic pyridine ring **89**. This kind of reaction can also be performed in recyclable polyethylene glycol (entry 4).[108]

Table 19



Entry	R^1	R^2	R^3	R^4	R^5	Conditions	Product, Yield (%)	Ref
1	Ar	Me	Ar	Thiophen-2-yl, Ph, OMe	CH_3, CF_3	L-proline (20 mol%), EtOH, reflux, 10-19 h	**88**, 70-85 (24 examples)	105
2	Ph	Ph	Ar	NHBn, NHTol, NH-propyl	Me	pTsOH.H_2O, DCM, rt, 4-7 d	**88**, 67-76 (7 examples)	106
3	Ar	Indol-3-yl	Ar, HetAr	Dimethyl-cyclohexanone, cyclopentanone, indanone		AcOH, 100-110 °C, 2 h	**89**, 68-77 (19 examples)	107
4	Ph	Me	Ar, HetAr	Cyclohexanone, dimethyl-cyclohexanone		PEG-400, 110 °C, TLC monitoring	**89**, 75-92 (27 examples)	108

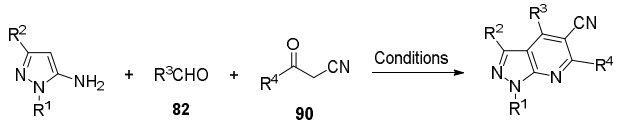
More complex polycyclic systems can be synthesized by using 2-hydroxy-1,4-naphtoquinone[109,110], 4-hydroxy-6-methyl-2*H*-pyran-2-one[111] or a mixture of 2-hydroxy-benzaldehydes with acetylacetic ester.[112]

5.3.6. MCR with aldehyde and 3-oxo-propanenitrile

An analogous 3-MCR reaction employs acyl-acetonitriles **90** instead of β-diketones as active methylene reagents in the presence of aminopyrazoles **V** and aldehydes **82**. This reaction therefore leads to trisubstituted pyridines **91** bearing a cyano group in position 5 (Table 20).[113-116] Although the detailed mechanism of this reaction is not fully elucidated, it is believed to rely also on a Knoevenagel condensation - Michael addition sequence. Shi *et al.* developed this reaction in a combinatorial fashion using ionic liquid as recyclable solvent (entry 1).[113] A library of 26 products **91** was obtained in good to excellent yields and the structure of one compound was confirmed by X-ray diffraction. The group of Rizk compared conventional heating and microwave irradiation and demonstrated that the latter conditions afforded better yields within a shorter time (entry 2).[114] More recently Hill (Bristol-Myers Squibb) reported the chemoselective synthesis of 1*H*-pyrazolo[3,4-*b*]pyridines from unbiased aminopyrazoles (R^1=H), while unbiased aminopyrazoles (R^1=H)

are usually leading to a pyrazolo[1,5-*a*]pyrimidines, with the help of $NaNO_2$ to perform the oxidation step (entry 3).[115] The impact of R^2 steric bulkiness on the selectivity was studied and *t*Bu appeared to slow the nucleophilic attack of *C*-4 to the point that pyrazolo[1,5-*a*]pyrimidines were obtained in significant amounts. The last example disclosed by Zhang & Liu describes the efficiency of graphene oxide anchored sulfonic acid (Fe_3O_4–GO–SO_3H) nanoparticles to catalyse this MCR using choline chloride (ChCl)/glycerol as solvent and microwave irradiation (entry 4).[116]

Table 20



v **82** **90** **91**

Entry	R^1	R^2	R^3	R^4	Conditions	Yield (%)	Ref
1	Me	Ph	Alk, Ar, HetAr	*t*Bu, Ph, C_6H_4*p*-Cl	[Bmim]Br, 80 °C, 5 h	80-98 (26 examples)	113
2	Ph	Pyridin-3-yl	C_6H_4*p*-OMe	Ar	AcOH, TEA, 150 °C, µW (500 W), 15 min	86-98 (6 examples)	114
3	H	Alk, Ar, HetAr, OH, Br	Ph, H, Alk	Ar, CO_2Et, HetAr, Alk	TEA, DMF, 90 °C then $NaNO_2$, AcOH, rt	19-80 (18 examples)	115
4	Ph	Pyridin-3-yl	Ar, HetAr	Pyridin-3-yl	$CoFe_3O_4$/GO–SO_3H, ChCl / glycerol, 80°C, µW, TLC monitoring	84-95 (15 examples)	116

5.3.7. Miscellaneous

Few metal-catalyzed reactions were recently reported to achieve the synthesis of pyrazolo[3,4-*b*]pyridines from amminopyrazoles with $Pd(OAc)_2$[117,118] or CuO.[119] There was also one report on microwave-assisted Wolff rearrangement of 2-diazo-1,3-dicarbonyl compounds.[120]

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