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Synthetic Accesses to 3/5-pyrazole Carboxylic Acids

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Abstract: This review attempts to sum up all the synthetic accesses to 3/5-pyrazole carboxylic acids or esters published, or patented, in the last 120 years. Many of them have demonstrated their robustness as well as quite large scopes. However, a majority are relying on the regioselectivity of reactions such as ketones deprotonations, cyclocondensations or [2+3] cycloadditions. For this reason, the preparation of original 3/5-carboxypyrazoles featuring a structure departing from the inherent regioselectivity of these synthetic accesses could be problematic. Moreover, a large scale synthesis of some 3/5-carboxypyrazoles could be a real challenge. It is thus reasonable to forecast that even more synthetic methodologies should be reported in the future in attempts to meet such requirements.

Keywords: Pyrazoles, side chain oxidation, cyclocondensation reactions, [2+3] cycloaddition reactions, diazomethane, ethyldiazoacetate.

The pyrazole-3/5-carboxylic acids or esters are fairly useful as synthetic intermediates or as compounds endowed with biological properties of interest [1]. Amongst the former (Fig. **1**), the most famous is probably ethyl 5-propyl-1*H*-pyrazole-3-carboxylate (**1**) as the starting material for the synthesis of Sildenafil (**2**), the selective inhibitor of type 5 cGMP phosphodiesterase present in Viagra [2]. Amongst amide derivatives of the latter, the cannabinoid antagonist Rimonabant (**3**) should be mentioned although its use as an antiobesity drug had to be discontinued recently [3-5]. A database survey points out that as much as 63000 different pyrazoles derivative are featuring a 3/5 carboxyl function; including about 5900 3/5-carboxylic acids. Many different preparations of pyrazole-3/5-carboxylic acids were used for this in the last 120 years and were explicitly reviewed once in the past [6]. Moreover, most of these synthetic routes are also included in much larger bodies of work describing pyrazole chemistry [7-9]. In the following, we have sought to review all the synthetic paths reported in the last 120 years and illustrate their potential scope. However, we did not attempt to mention every single example reported as such work would be beyond the scope and size of this review.

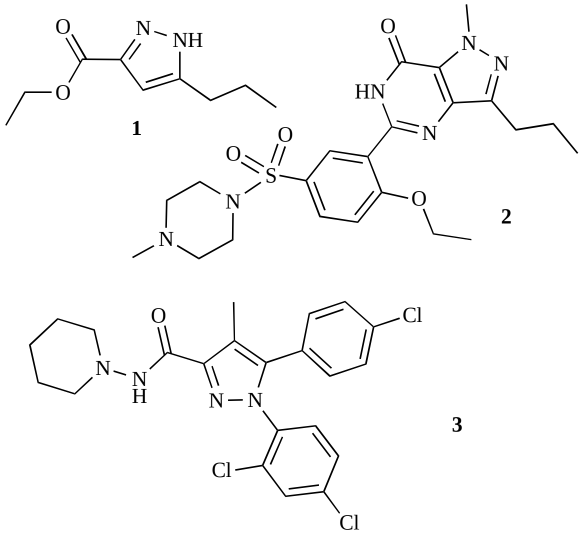
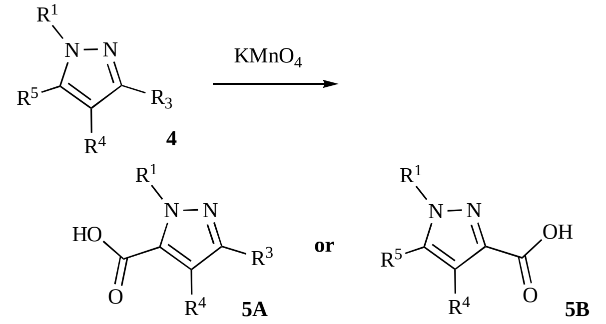


Fig. (1).



R^1	R^3	R^4	R^5	Ref.
Ar	CO_2Et	H	2-furanyl	A [21]
Me	C_nF_{2n+1}	H	2-furanyl	A [22]
Me	Me	Cl	H	A [23]
Me	H	H	Me	A [24]
Ph	CO_2H	H	Bu	A [25]
Ph	Me	H	2-furanyl	A [11]
Bn	Me	H	2-furanyl	A [11]
H	Me	Br	H	B [23]
H	Me	NO_2	H	B [26]
H	Me	I	H	B [27]
H	Me	Ph	H	B [28]
Me	Me	Cl	H	B [23,29]
Ph	CO_2H	H	Et	B [10,30]
H	2-furanyl	H	tBu	B [11]
H	2-furanyl	H	Me	B [11]
H	Me	Ph	Ph	B [12,27]
H	PhCO	Ph	CO_2H	B [16]
Ph/Me	MeCO	Me	H	B [14, 15]
H	2-furanyl	H	Ph	B [17]
H	Me	H	3-pyridyl	B [31]
H	3-pyridyl	H	Ph	B [17]
H	5-(3-methyl isoxazoyl)	H	Ph	B [17]
H	2-thienyl	H	Ph	B [18]
H	Me	NO_2	4-NO_2-Ph	B [18]

Scheme 1.

As depicted in Scheme **1**, the controlled side-chain oxidation of pyrazoles **4** with potassium permanganate is amongst the oldest synthetic method described [10]. Scheme **1** illustrates the variety of derivative **5A/B** prepared. Water is the solvent most often used although the use of mixture of acetone and benzene [11] or water

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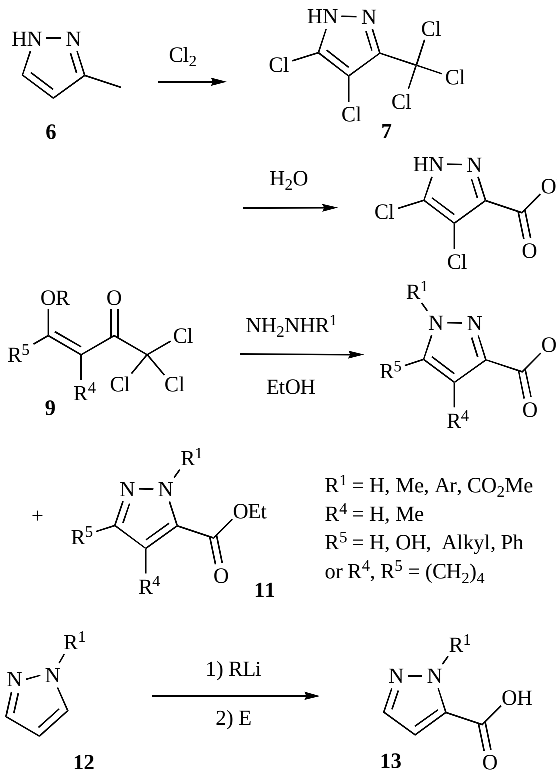
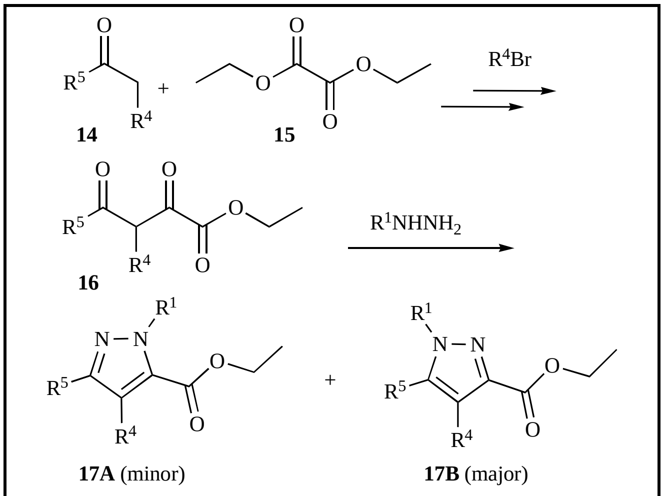


Scheme 2.

and tertbutyl alcohol [12] has been described. In the latter case, this was reported to be instrumental; as shown by a control experiment in water only [12]. Moreover, a patent describes such oxidations in sulfuric acid using "a metal salt of variable valence" along with ozone [13]. The 3/5-methylpyrazoles are the most used substrates although, as shown in Scheme **1**, other groups such as an acetyl (oxidized with hypobromite [14] or hypoiodite [15]) or a benzoyl (oxidized with peracetic acid) [16] can be subject to an oxidation. Various 3/5-heteroaryl moieties of pyrazoles such as thienyl, pyridyl, isoxazoyl [17,18] or furanyl [11] as well as the pyridine part of pyrazolo[1,5-a]pyridines [19] can be oxidized to a 3/5-carboxylic component with permanganate. Moreover, in a number of examples, 2-furanyl groups were oxidized with catalytic amount of ruthenium III chloride and sodium periodate [20-22].

As shown in Scheme **2**, the extensive chlorination of 3-methyl pyrazole (**6**) leads to compound **7** which, upon hydrolysis of the trichloromethyl group, provides an access to the 4,5-dichloro-1*H*-pyrazole-3-carboxylic acid (**8**) [29]. Few more examples of such hydrolysis were reported [32-34] and further work from many haloacetylated enol ethers **9** extended this approach to a variety of derivatives **10** and **11** [35-40] as well as few carboxamides [41]. This is actually the synthetic path used to produce the 3-carboxypyrazoles ester **1** mentioned in the introduction [37]. The carbon 3/5 deprotonation of unprotected [42] (in low yield) or of N-protected (in better yields) pyrazoles **12** with groups such as phenylsulfonyl [43,44] or tosyl [45,46], 2-(3-chloropyridyl) [47], 4-methoxybenzyl [48] or hydroxymethyl [49], followed by the addition of carboxyl precursors is another method to prepare some pyrazole acids (or esters). Interestingly, a study with various N1-alkylpyrazoles points out that their deprotonation, selectively takes place only on position 5 and leads to derivative such as **13** [50].

Scheme **3** depicts another, very ancient [24,51-54] and far more used, method which starts with condensations between various ketones anions **14** (often methyl bearing ketones; i.e.: R^4 = H or cyclic compounds) and diethyl oxalate (**15**) leading to many β-diketone esters **16**. In few instances, further alkylation reaction led to more elaborate β-diketone esters **16** featuring an additional substituent ($R^4 \neq H$) [55]. Then, upon the addition of hydrazines or hydrazines salts on these intermediates, a vast array of pyrazole-3-carboxylic esters **17A/B** can be prepared. Interestingly, when using substituted substituted hydrazines, the minor isomers with the formula **17A** is sometime reported [30,56-58]. Moreover, a complete inversion of this regioselectivity is possible when condensing 2-oxime derivative of some of these β-diketone esters and substituted hydrazines [57]. The use of N-methoxy-N-methyl-β-enaminoketo-esters as starting material for this condensation reaction also allows a control of its regioselectivity [59].

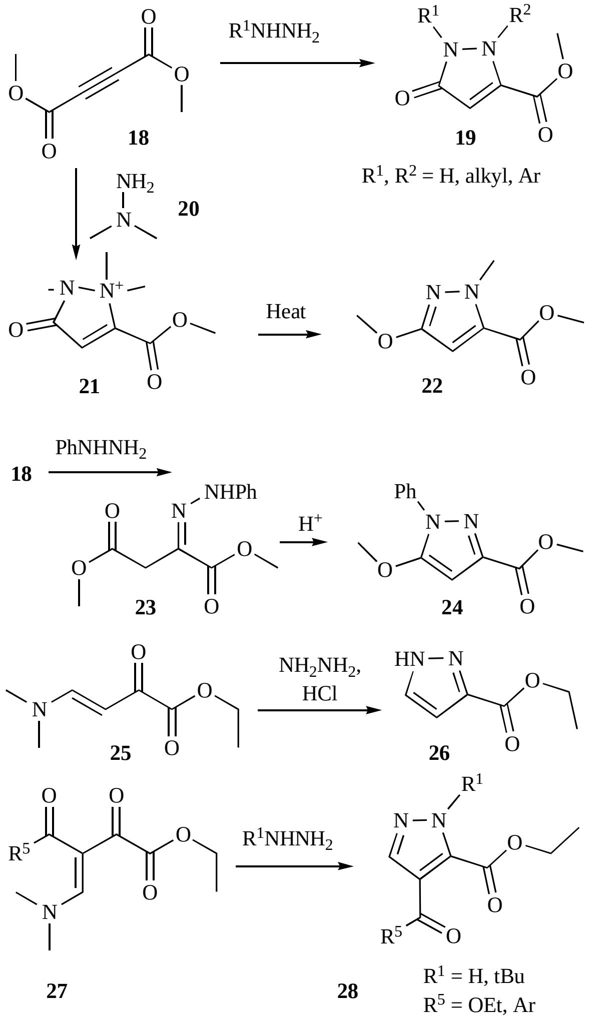


R^1	R^4	R^5	Ref.
H	H	CH_2COCH_3	B (5-5'dimer) [52]
H	H	nBu	B [25]
H	-O-CH_2-CH_2-		B [60]
H	-$CH_2CH_2CH_2$-		B [60-62]
H	-(Me-C_3H_5)-		B [63]
H	-$CH_2CH_2CH_2CH_2$-		B [54,60,62]
H	H	Ar	B [53,60,62,64,65]
H	H	CH_2Ar	B [60]
H	H	CH_2CH_2Ar	B [60]
H	H	Alkyl, Ar	B [60,66,67]
H	H	Me	B [68]
Ph	H	OH	B [51]
H	H, Me	OEt	B [69]
H	Me	Et	B [70]
H	6-Cl-piperonyl	Ar	B [55]
H	H	2-Benzofuranyl	B [71]
Bn	-$CH_2CH_2CH_2CH_2$-		A and B [54]
Me	-$CH_2CH_2CH_2CH_2$-		A and B [54]
Me	H	Me	A and B [24,72,73]
Ar	H	Ar	A and B [56,58]
CH_2Ar	H	Ar	A and B [74]
Ph	H	Et	A and B [30]
Ph	H	Bu	A and B [57]

Scheme 3.

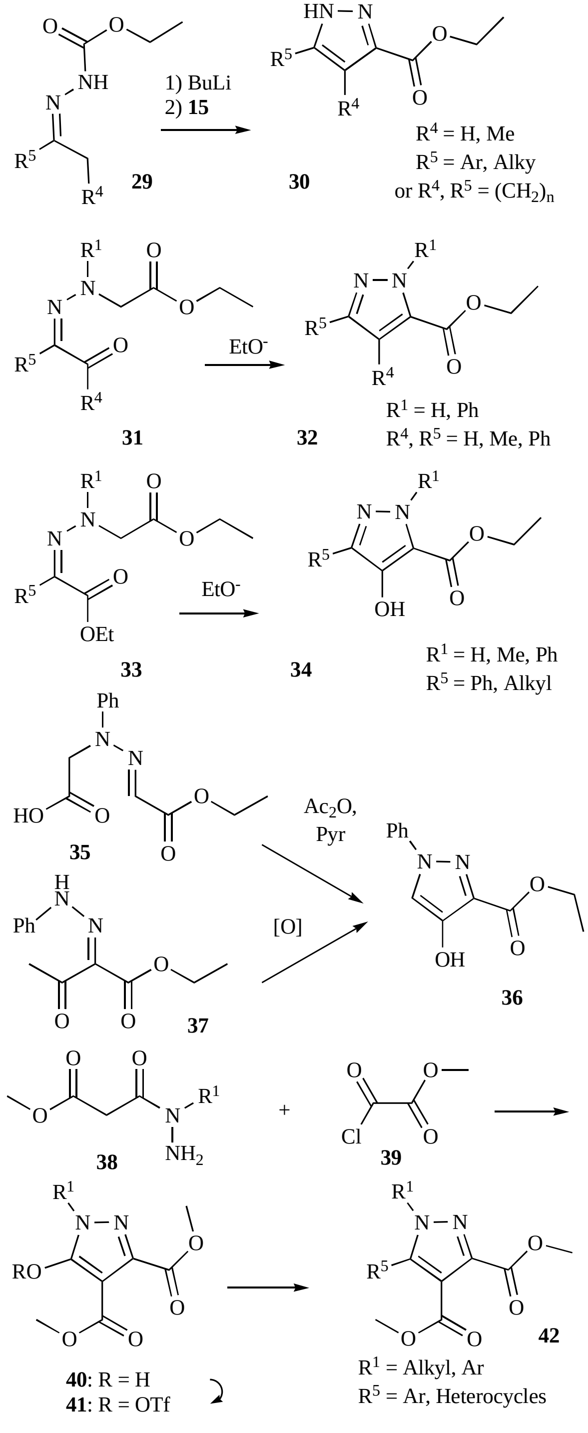
The additions of hydrazines on many highly functionalized compounds such as β-aroylacrylic acid epoxides [75] or carboxyalkynylketones [76-78] are also providing accesses to pyrazole-3-carboxylic acids or esters. As depicted in Scheme **4**, the condensation between the dimethylacetylenedicarboxylate (**18**) and hydrazine [79,80], monosubstituted hydrazines [81-84] or 1,2-

disubtituted hydrazine [85] provides the corresponding 5-oxo-3-carboxypyrazoles **19**. On the other hand, the addition of 1,1-dimethylhydrazine (**20**) leads to the pyrazolium **21** which, upon heating, undergoes a rearrangement into the O,N- dimethylated ester **22** [81,86]. Moreover, the addition of phenylhydrazine on compound **18**, leads to **23** which, following a cyclization in acidic condition, provides the 5-methoxy-1-phenyl isomer **24** [87]. Interestingly, this compound is also isolated from the reaction between **18** and a phosphazene [88]. The condensation of dimethylformamide dimethylacetal on ethylpyruvate leads to the Mannich base **25** which can undergo the addition of hydrazine hydrochloride to give pyrazole **26** [89]. Few other related bases such as **27**, made from condensation reaction with dimethylformamide dimethylacetal [89] or via the C-acylation of enaminones by ethyl oxalylchloride [90] have been reported. These are also leading to pyrazole esters **28** upon addition of hydrazines [89,90].



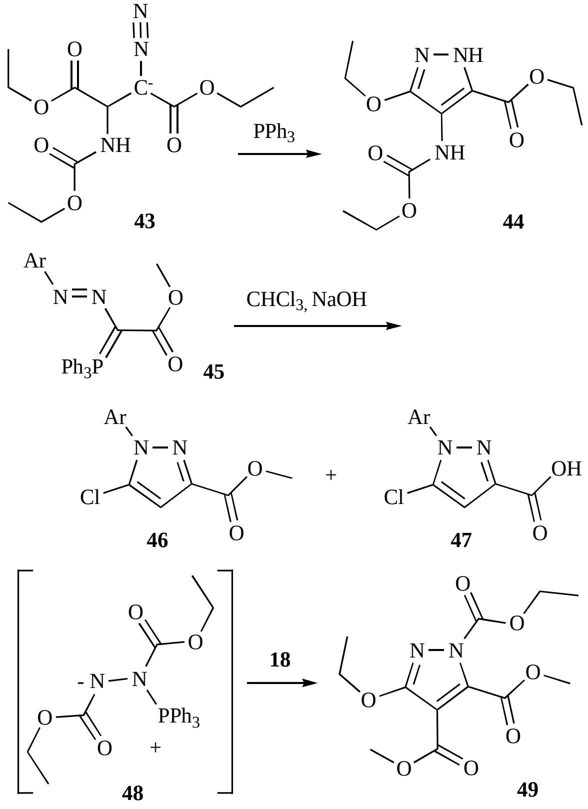
Scheme 4.

A recent synthetic access, also involving diethyl oxalate (**15**), requires its condensation with hydrazones **29** under strongly basic conditions and leads to a vast array of pyrazoles esters **30** [91] (Scheme **5**). Moreover, few suitably substituted hydrazones such as **31** or **33** lead, upon a ring closure, to pyrazoles-3-esters **32** [92] or the 4-hydroxy analogues **34** [93,94]. A quite remarkable cyclization of compound such as **35** takes place upon treatment in acetic acid in pyridine and provides an access to many pyrazoles including the 3-carboxy-4-hydroxy derivative **36** [95]. The same derivative is also obtained upon oxidation of the methyl moiety of compound **37** using the hypervalent [hydroxy(tosyloxy)iodo]benzene followed by a based-induced cyclization [96]. Older reports actually describe similar approaches: from tetronic acid in a few synthetic steps [97], from the basic cyclization of the brominated homolog of **37** [98] or upon monobromination of **37** followed by its cyclization [99]. Interestingly, the latter approach provides an access to the 5-brominated derivative of **36** upon cyclization of the dibrominated derivative of **37** [99]. A sequential approach was also reported in order to prepare 1-substituted-5-hydroxy-3-carboxylate derivatives such as **40**. These were prepared *via* the condensation of the malonichydrazides **38** and oxalyl chloride (**39**). The subsequent triflation of the 5-hydroxyl function of compounds **40**, to give the building blocks **41,** allowed the construction of a vast array of carboxypyrazoles **42** *via* Suzuki-Miyaura reactions on the R^5 position [100].



Scheme 5.

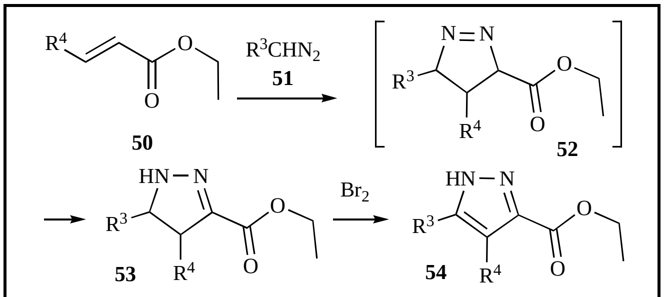
As shown in Scheme **6**, the reductive power of triphenylphosphine allows the cyclization of the azomethide **43**, via a Wittig-related condensation on its ester moiety, into the 4-aminated carboxypyrazole **44** [101]. In a different approach, two units of carbene, generated from chloroform and sodium hydroxide under phase transfer conditions, react with the arylazomethylenephosphoranes **45**. This provides a very unique access to the 5-chlorinated esters **46**, along with the corresponding acids **47** resulting from further reaction with sodium hydroxide [102]. The addition of triphenylphosphine to diethylazodicarboxylate allows the generation of the reactive dipole **48** which can add to dimethylacetylenedicarboxylate (**18**) to give, *via* a [2+3] cycloaddition, the highly substituted carboxypyrazole **49** [103].



Scheme 6.

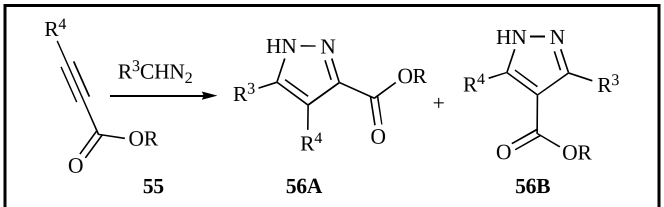
Many other [2+3] cycloadditions are leading to carboxypyrazoles. As depicted in Scheme **7**, the reaction of acrylates **50** with diazoalkanes **51** leads regioselectively to the intermediates **52**. This rearranges into the pyrazoline **53** and upon treatment with bromine, gives the 4-substituted 3-pyrazole esters **54**. From 3-aryl-2,3-dehydro amido esters, a similar cycloaddition was reported and the product does not require an oxidation step to provide the pyrazole ring as elimination of the amide readily takes place [104]. A similar approach was investigated from acetylthioacrylates although, following the formation of the pyrazole, its N-methylation by the excess of diazomethane present was also noted [105].

As seen in Scheme **8**, from propiolates **55**, the same [2+3] cycloaddition does not require an oxidation step to obtain the pyrazoles **56A/B**. However, the orientation of this cycloaddition is very much dependent on the nature of R^4 and isomers **56B** are also obtained, sometime as the major products. For instance, an alkyl group orients toward **56A**; whereas attracting groups such as a phenyl or a formyl do lead to the occurrence of substantial amount of the isomer **56B** [113,114]. Moreover, the use of an excess of diazomethane can lead to the methylation of the pyrazole nitrogens [113,114].



R^3	R^4	References
H	H, Me	[62,104,106-108]
H	Ph	[62,106,109]
H	Et, Pr	[110]
Me	H	[109]
H	CO$_2$Et	[109]
CO$_2$Me	Ph	[111,112]
H	Ar, heterocycle	[104]

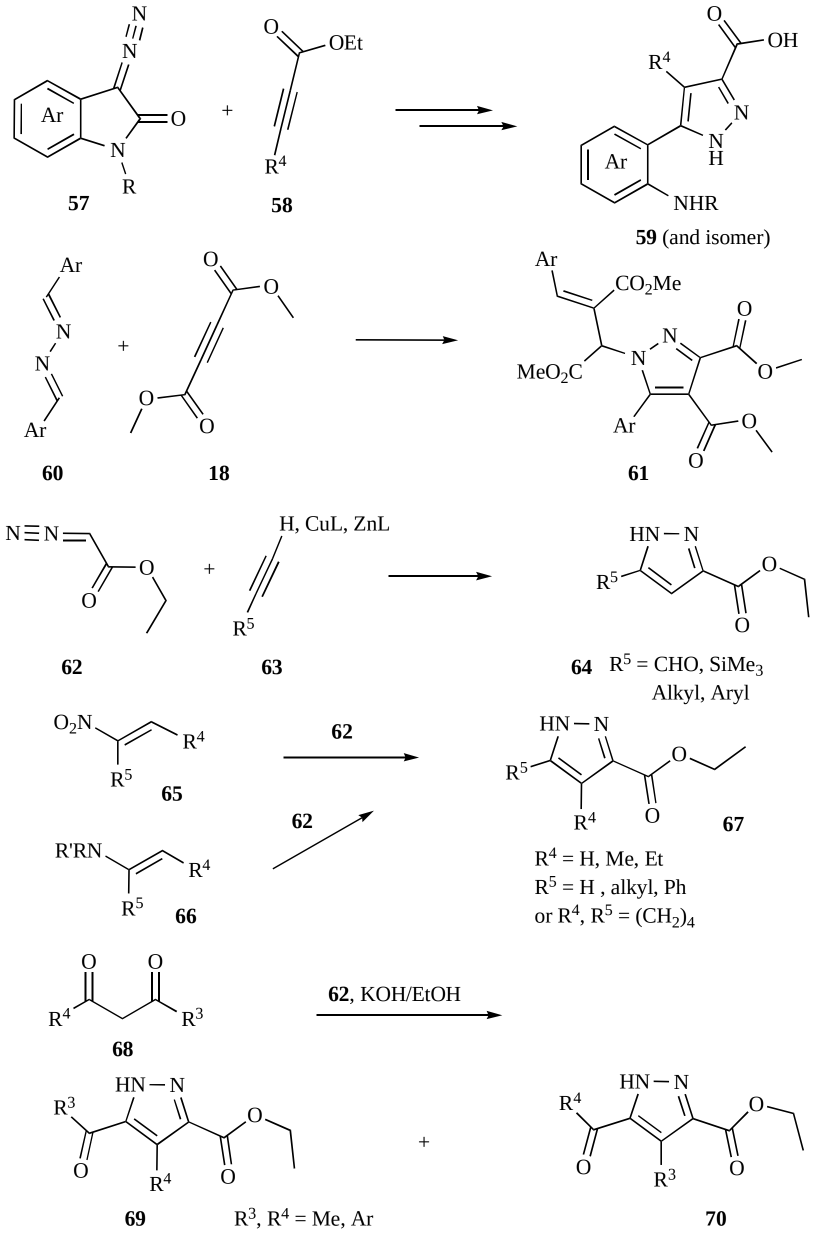
Scheme 7.



R^3	R^4	R	Formula and Reference
H	Ph	Me	A, B [114]
CO$_2$Me	H	Me	A [115]
CO$_2$Et	Ph	Me	A, B [114]
H	Me	Et	A [114]
H	CH(OMe)$_2$	Me	A [113]
H	CHO	Me	A, B [113]
H	CH$_2$OH	Me	A, B [113]
CO$_2$Et	CH(OMe)$_2$	Et	A [113]
CO$_2$Et	CHO	Et	A, B [113]
CO$_2$Et	CH$_2$OH	Et	A, B [113]
(CH$_2$)$_n$CO$_2$Me	H	Me	A [116]
(CH$_2$)$_n$CO$_2$Me	CO$_2$Me	Me	A [116]
CH$_2$O(CH$_2$)$_2$OBn	H	Me	A [117]
H	C$_n$F$_{2n+1}$	Et	A [118,119]
CF$_3$	H	Me	A [120]
CH(OMe)$_2$	H	Me/Et	A [121,122]

Scheme 8.

Scheme **9** depicts an interesting rearrangement, involving a ring expansion, taking place when heating diazoindol-2(3*H*)one such as **57** and propiolates **58**. Following an hydrolysis, this leads to an array of acids **59** [123]. A remarkable [2+3] cycloaddition process takes place between aldehyde azines **60** and two equivalents of dimethylacetylenedicarboxylate (**18**) since heating them together leads to pyrazoles **61** [124]. The carboxyl moiety of 3/5-carboxypyrazoles can also come from the dipole part of this reaction as cycloadditions of ethyldiazoacetate (**62**) with various alkynes **63** lead to products **64** [111,119,125,126]. An intramolecular version of this reaction was also investigated [127]. Moreover, many copper acetylides provide starting compounds, *via* their reac-

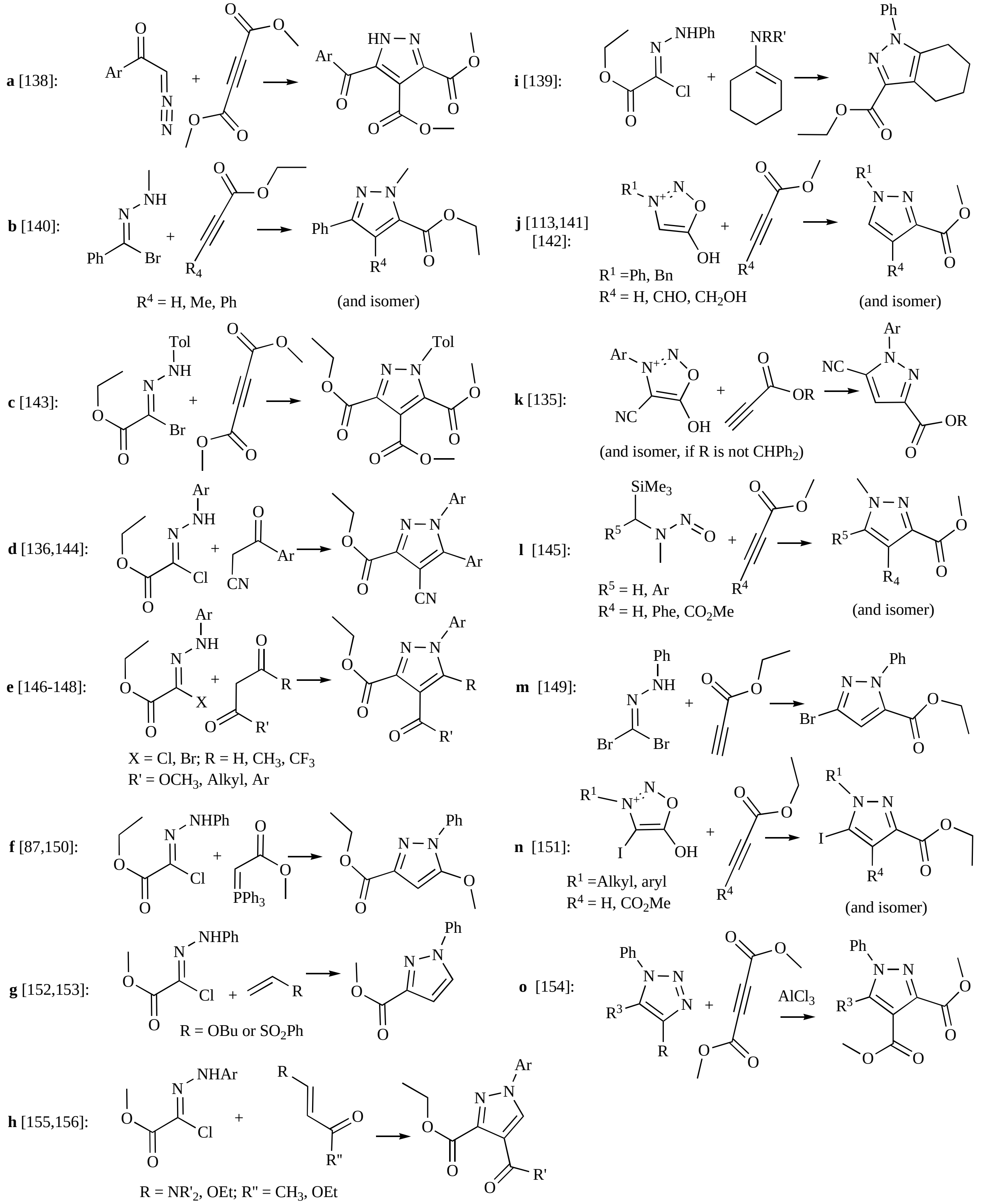


Scheme 9.

tion with benzyldiazoacetate, for a vast array of benzyl esters equivalent to **64** [128]. More recently, zinc acetylides were reported to react with **62** and also lead to many examples of **64** [129]. Such [2+3] cycloadditions also proceed from mostly bis-substituted nitrovinyl derivatives **65** [28,130] as well as from enamines **66** [131,132] to give pyrazoles **67**. In one instance, an ynamine was also used [115]. The anions of β-diketones such as **68**, probably under their enolate forms, also react with ethyldiazoacetate (**62**) although the regioselectivity can be an issue as mixture of **69** and **70** are isolated when relevant (i.e.: $R^3 \neq R^4$) [16,133,134].

Scheme **10** illustrates that quite a few dipolarophiles differing from the one described above can react with an array of dipoles and provide original accesses to 3/5-carboxypyrazoles. From propiolates and various dipolarophiles, usually generated *in situ* (entries **a-c** and **j-o**), 3/5-carboxypyrazoles are obtained although, as for the cycloadditions described in Scheme **8**, fairly often along with the corresponding isomeric 4-carboxypyrazoles (entries **b**, **j**, **l** and **n**). The regioselectivity is again very much dependant on the R^4 group of the propiolates and follows the same trends described in Scheme **8**. Interestingly, as depicted in entry **k**, the occurrence of the isomeric 4-carboxypyrazole was seen only if the alcohol moiety of the propiolate was smaller than a benzydryl [135]. The carboxyl function of the pyrazole can also be provided by nitrilimines, generated *in situ* by the basic treatment of 2-halogeno-2-(2-arylhydrazono)acetates. These undergo cycloadditions with most of the dipolarophiles (entries **c-i**). Entry **d** is actually the synthetic route mentioned in one of the patent [136] describing the synthesis of Rimonabant (**3**) depicted above. With this type of dipole, the occurrence of the isomeric 4-carboxypyrazole is usually avoided. Interestingly, from halogenated sydnone (entries **m**) or bromonitrilimine (entry **n**), fairly rare 3/5-halogenated-5/3-carboxypyrazoles are obtained. Moreover, a traceless method was also designed *via* cycloadditions with polymer-supported α-silylnitrosoamides related to the reagent depicted in entry **l** [137].

Last but not least, as depicted in Scheme **11**, a 50 year-old report [16] mentioned the occurrence of very small amount of 4-phenylpyrazole-3-carboxylic acid (**72**) arising from the reaction

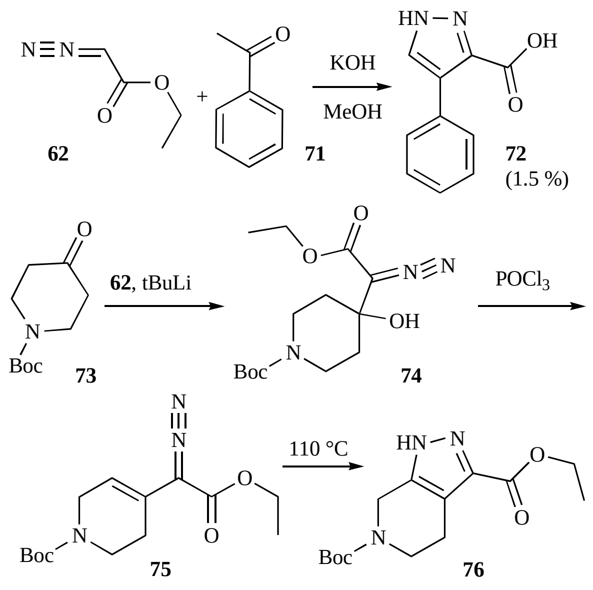


Scheme 10.

between ethyldiazoacetate (**62**) and acetophenone (**71**) under basic conditions. Interestingly, recent patents [157,158] may provide a mechanism, differing from a [2+3] cycloaddition, for this reaction. Indeed, these patents describe the condensation of the anion of ethyldiazoacetate (**62**) on piperidinone **73** which lead to the tertiary alcohol **74**. Upon a dehydration reaction, using phosphorus oxychloride, compound **75** is then obtained and undergoes a cyclization into the pyrazolo[3,4-c]pyridine **76** in boiling toluene.

CONCLUSION

At least 20 different types of synthetic routes to 3/5-carboxypyrazoles have thus been reported in the last 120 years.



Scheme 11.

Many of them have demonstrated their robustness as well as quite large scopes. However, a majority are relying on the regioselectivity of reactions such as ketones deprotonations, cyclocondensations or [2+3] cycloadditions. For this reason, the preparation of original 3/5-carboxypyrazoles featuring a structure departing from the inherent regioselectivity of these synthetic accesses could be problematic. Moreover, a large scale synthesis of some 3/5-carboxypyrazoles could be a real challenge. It is thus reasonable to forecast that even more synthetic methodologies should be reported in the future in attempts to meet such requirements.

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