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3-Pyrazolines (2,3-dihydro-1*H*-pyrazoles): synthesis, reactivity, and physical and biological properties

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This paper is intended to honor Professors Alan R. Katritzky (Norwich & Gainesville), André Maquestiau (Mons) and Robert Jacquier (Montpellier) for their outstanding contributions to heterocyclic chemistry

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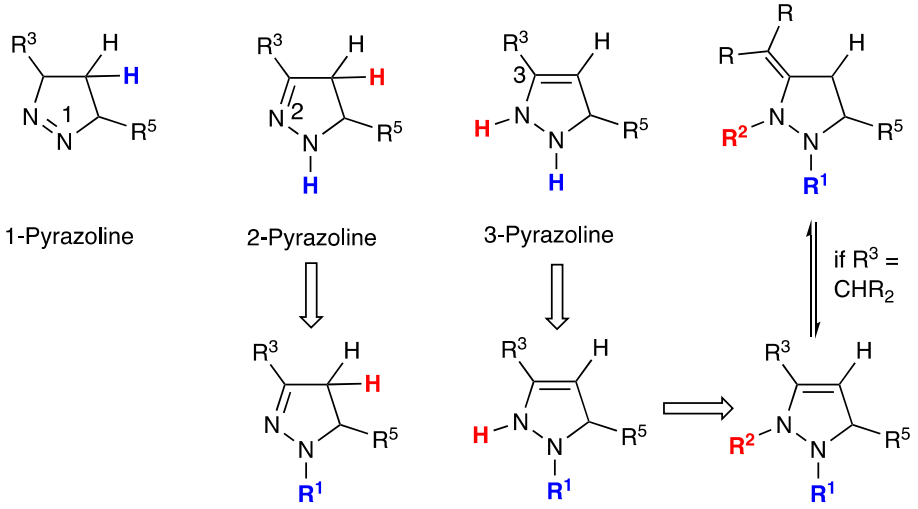
Abstract

This account provides a summary of the current knowledge on 3-pyrazolines, an important but rather neglected field of heterocyclic chemistry. The review is divided into sections on the synthesis, reactivity, structure and biological properties and covers the literature from 1937 to 2020. In an effort to clarify some results, theoretical calculations were carried out anew.



Keywords: Pyrazolines, dihydropyrazoles, tautomerism, protonation, NMR, X-ray structures

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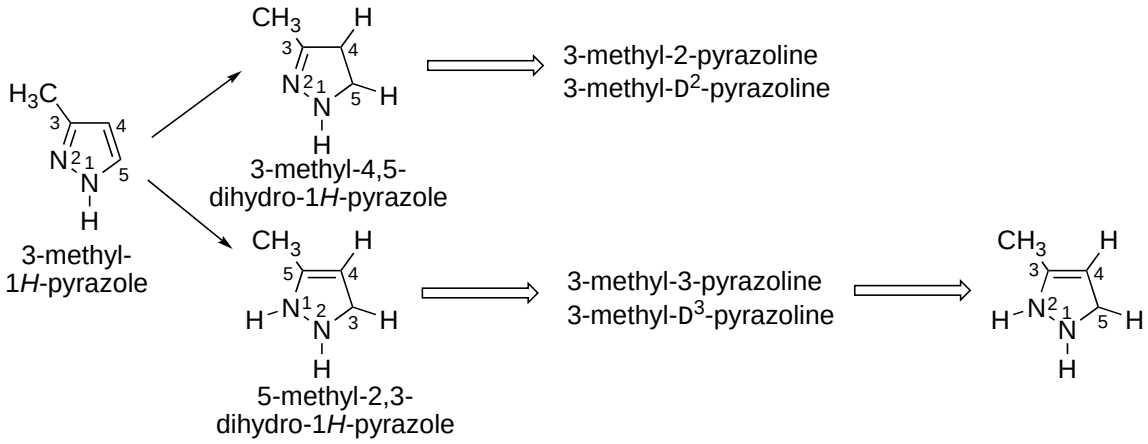
1. Introduction

The compounds that are the subject of this review are called 3-pyrazolines, although they were previously known as Δ^3-pyrazolines – similarly 2-pyrazolines were known as Δ^2-pyrazolines. The IUPAC prefers the use of the Hantzsch–Widman nomenclature, in which these compounds are called dihydropyrazoles (Scheme 1).



Scheme 1. Nomenclature and atom numbering.

The two nomenclature systems coexisted but finally the IUPAC abandoned the pyrazoline names and accepted the dihydropyrazole ones. However, pyrazoline continues to be used (for instance by the NIST), probably because it is shorter and more intuitive. The main advantage of the old names is that the numbering of the atoms is the same for 2-pyrazolines, for instance a 3-methyl substituent in a 2-pyrazoline maintains the numbering in a 2,3-dihydro-1*H*-pyrazole but not for 3-pyrazolines, e.g., 3-methyl-3-pyrazoline corresponds to 5-methyl-2,3-dihydro-1*H*-pyrazole. A search of the literature affords compounds that are named 3- or 4-pyrazolines but are actually 2-pyrazolines,[1-6] or 1-pyrazolines[1,7-11] and 2,3-dihydro-1*H*-pyrazoles when they are 4,5-dihydro-1*H*-pyrazoles. This discrepancy in nomenclature made it difficult to search databases.[12] Even in the Cambridge Structural Database[13] there is at least one product (Refcode YAKYAK, no hydrogen atoms, Figure 1) that it is represented as a 3-pyrazoline **1** with an NH on N2 when the structure is that of a 2-pyrazoline **2** (with characteristic distances for the N1–N2–C–C fragment). It is worth noting that the authors reported this compound as the 2-pyrazoline **2**.[10] The structure of YAKYAK will be discussed again in Section 3.2.

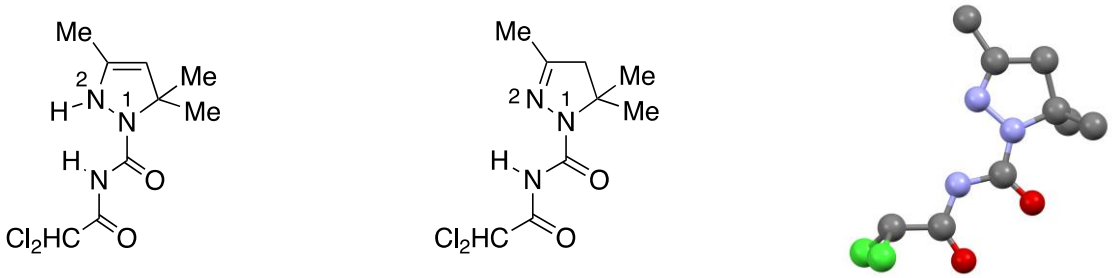
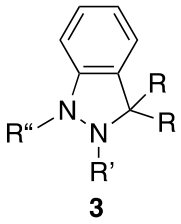


Figure 1. The structures of YAKYAK.

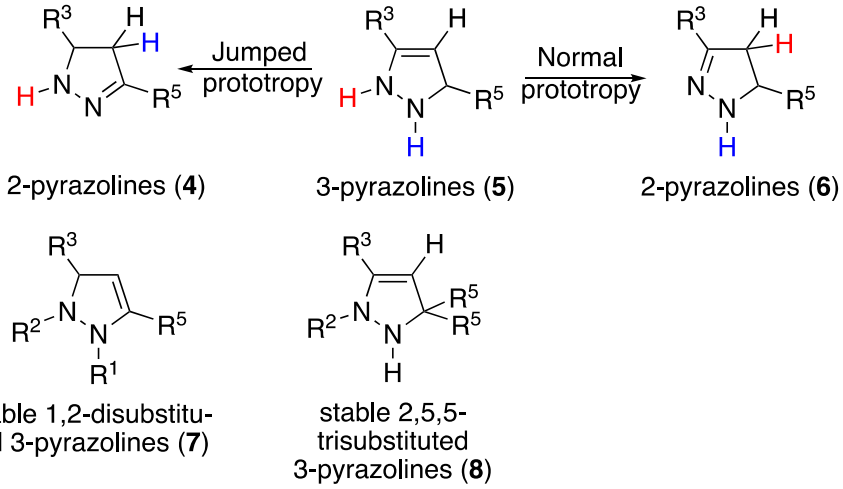
In the present review we decided to use the names 2-pyrazolines and 3-pyrazolines. Furthermore, the 2,3-dihydro-1*H*-indazoles (**3**), *i.e*., compounds in which the CC double bond is part of an aromatic ring (Figure 2), are excluded due to the loss of the enamine (or ene-hydrazine) reactivity of 3-pyrazolines as well as their character as a dipolarophile.



3

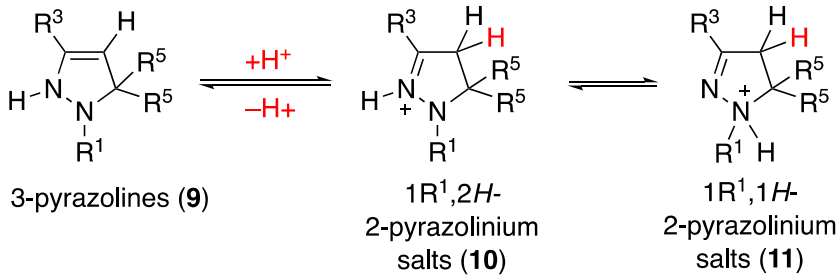
Figure 2. 2,3-Dihydro-1*H*-indazoles.

Pyrazoles, their oxidized derivatives, pyrazolones, and their reduced ones, pyrazolines and pyrazolidines, all form part of classical heterocyclic chemistry. Pyrazoles and pyrazolones are stable but pyrazolidines and, in particular, pyrazolines are easily oxidized. In addition to the sensitivity to oxidation, 3-pyrazolines **5** could isomerize to 2-pyrazolines **4** or **6** if substituents do not prevent this process, as in structures **7** and **8** (Scheme 2). This aspect will be discussed in detail in Section 3.2.



Scheme 2. Prototropy and stability.

One final – but important – aspect of the chemistry of 3-pyrazolines is the acid-base relationship with 2-pyrazolinium salts (Scheme 3). Several mechanisms to obtain 3-pyrazolines **9** proceed via 2-pyrazolinium salts, either directly from **10** or, after prototropy, from **11**.

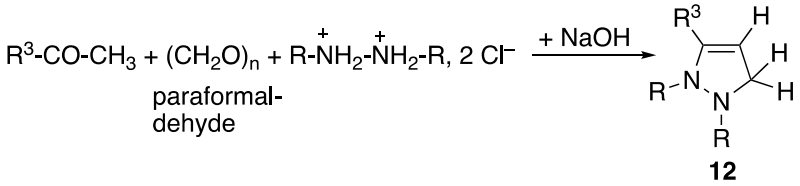


Scheme 3. Relationship between 3- and 2-pyrazolines through their pyrazolinium salts.

2. Synthesis

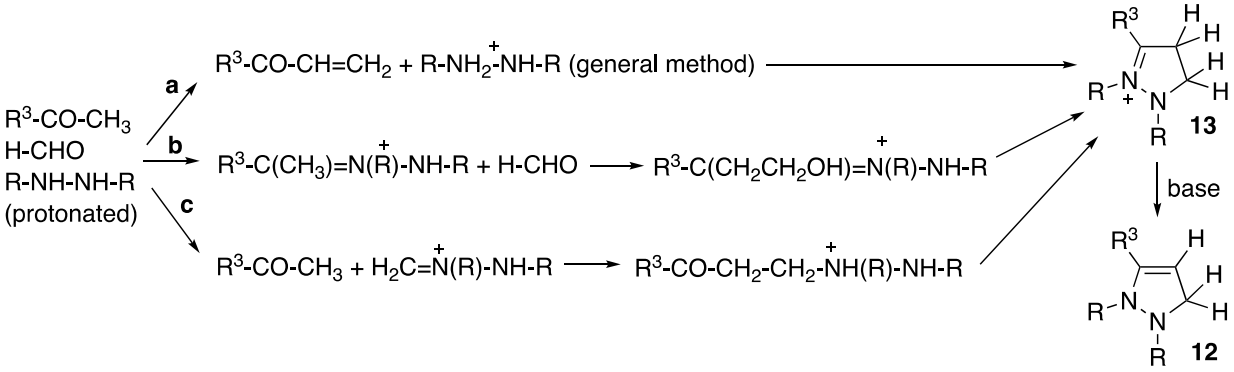
2.1. From hydrazines and their derivatives [(NN) + (C) + (CC)] and [(NN) + (CCC)]

2.1.1. Simple alkyl and aryl hydrazines. Curiously, the first reported synthesis of a 3-pyrazoline was a three-component reaction although it was not recognized as such;[14] this process is related to the Mannich reaction (replacing a secondary amine by a hydrazine) and it was reported by Hinman and subsequently became known as the Hinman reaction (Scheme 4).[15] In this synthesis a carbonyl compound, like benzophenone, reacts with paraformaldehyde and 1,2-dimethylhydrazine dihydrochloride to afford pyrazoline **12**. On using cyclanones, formaldehyde and 1,2-dimethylhydrazine the corresponding 1,2-dimethyl-3,4-polymethylene-3-pyrazolines were obtained.[16]



Scheme 4. Hinman reaction [(NN) + (C) + (CC)].

The mechanism (Scheme 5) was elucidated by Aubagnac *et al*.[17] through a series of experiments and using literature results on the synthesis of 2-pyrazolines. The conclusion was that the reaction follows pathway **c** in Scheme 5. The pyrazolinium salt **13** is the common intermediate in all of the hypothetical mechanisms.



Scheme 5. The three possible mechanisms of the Hinman reaction.

The Hinman method was widely used[18-20] but it was soon superseded by the general method in which unsaturated carbonyl compounds (often α,β-unsaturated ketones) react with 1,2-substituted hydrazines with a stoichiometric amount of a protic acid or an acid catalyst to afford 3-pyrazolines **12**; In some cases the intermediate 1,2-disubstituted-2-pyrazolinium salts **13** were isolated. In the case of the Hinman reaction, formaldehyde can be replaced by another molecule of the same ketone to give 1,2,3,5,5-trisubstituted 3-pyrazolines (pyrroles are also formed).[21-23] One of the steps in the preparation of 3-pyrazolinium cations **13** took place by a disrotatory process.[23] The transformation of **13** into **12** by the action of NaOH involves a 3-hydroxy-pyrazolidine **14** (Figure 3).[24,25]

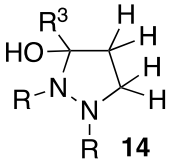
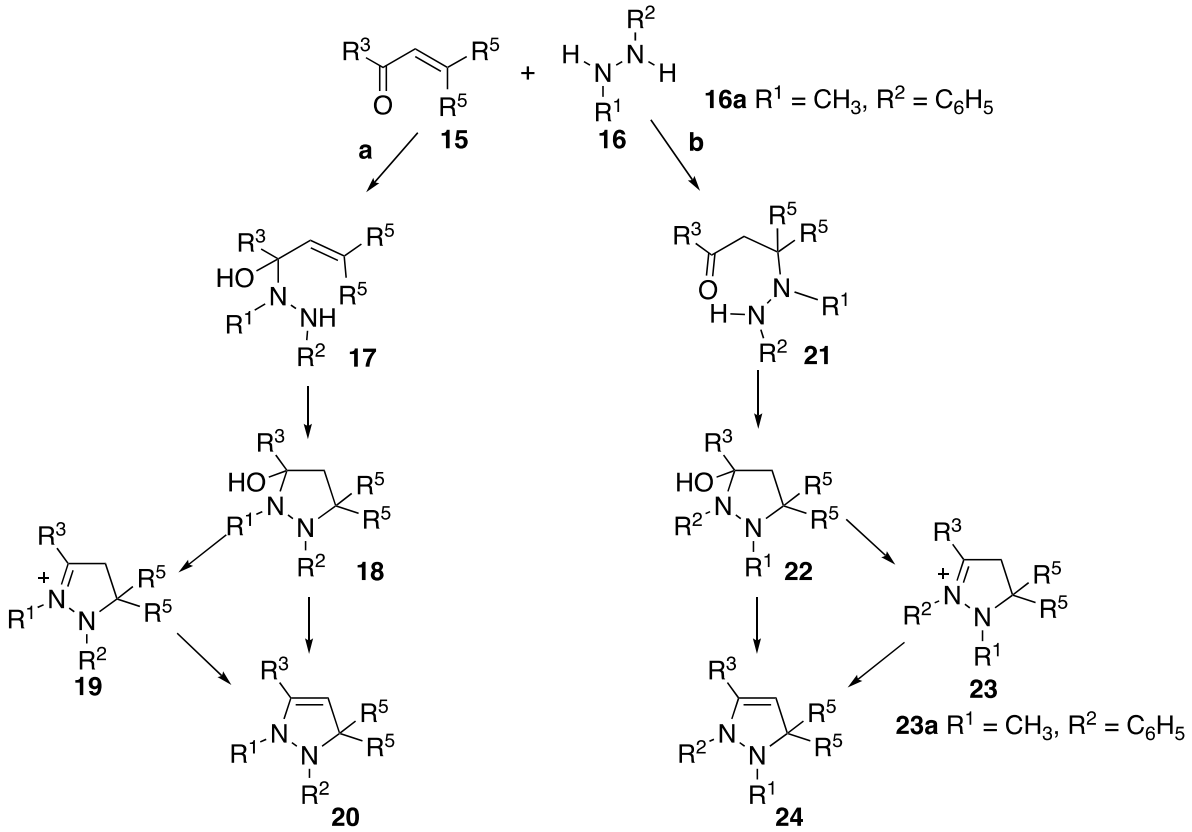


Figure 3. Structure of the 3-hydroxy-pyrazolidine **14**.



Scheme 6. Mechanism for the formation of 3-pyrazolines from α,β-unsaturated carbonyl compounds [(NN) + (CCC)].

The mechanism for the formation of **13** is the same as that for 2-pyrazolines. For a long time[26] it was not clear which of the two NC bonds was formed first, i.e., **17** or **21** (Scheme 6). However, in 1970 it was established, using 1-methyl-2-phenylhydrazine (**16a**), that the initial step in the mechanism is a 1,4-addition of the more nucleophilic NHMe on the double bond of **15** (Scheme 6, pathway **b**). This was confirmed by Kenny and

Robinson[27,28] in the reaction between chalcone and phenylhydrazine to give 1,3,5-triphenyl-2-pyrazoline using Baldwin's rules (5-*exo*-*trig* is a favored ring closure while 5-*endo*-*trig* is not favored)[29] and a very elegant labeling with ^{13}C on the chalcone and ^{15}N on the phenylhydrazine. It should be noted that in Scheme 6 both pathways lead to the same compounds (pairs **18**/**22**, **19**/**23**, and **20**/**24**) when $R^1 = R^2$. Although Kenny and Robinson were not cited,[27,28] other authors employed Baldwin's rules to explain the results obtained with methylhydrazine (**21**, $R^1 = CH_3$, $R^2 = H$).[30]

The use of Baldwin's rules by Kenny and Robinson[27,28] was questioned by List in 2010; he suggested that a more plausible mechanism would involve a pericyclic 6π-electrocyclization.[31] Although both mechanisms will lead to different stereoisomers, the *N*-phenyl inversion will make them indistinguishable (Figure 4). We proposed the List electrocyclic mechanism for the synthesis of 2- and 3-pyrazolines in 1971 in a review entitled 'Synthesis and reactivity of pentagonal heterocycles: electrocyclic reactions and sigmatropic rearrangements".[32]

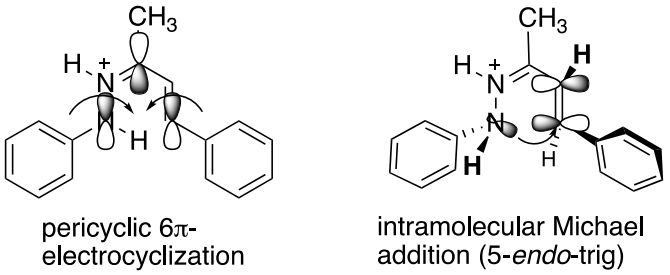
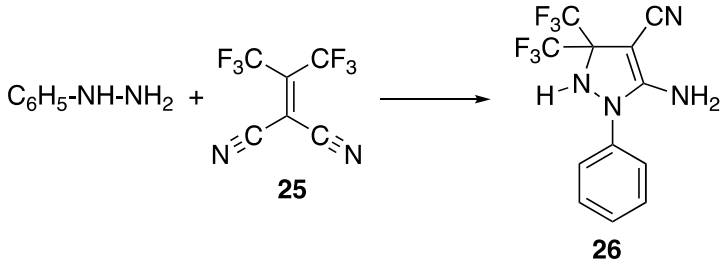


Figure 4. Two possible mechanistic scenarios.

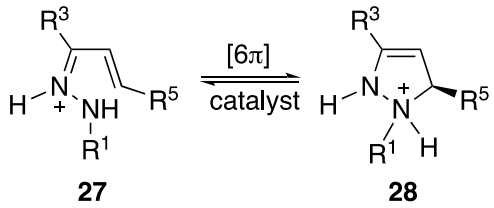
Both the Hinman [(NN) + (C) + (CC)] and Aubagnac [(NN) + (CCC)] methods were used by Kostyanovsky *et al*. to prepare the sterically hindered 3-pyrazolines that were required to study their nitrogen inversion.[33,34]

1,3-Difunctional compounds (β-dicarbonyls, β-ketoesters, and similar compounds) react with hydrazine to afford different types of pyrazoles. Amongst them are malononitriles that yield 3,5-diamino-1*H*-pyrazoles.[26,35] Starting from a special derivative **25**, 3-amino-2-phenyl-5,5-bis(trifluoromethyl)-3-pyrazoline-4-carbonitrile **26** was obtained (Scheme 7).[36] Compound **26** belongs to class **8** (Scheme 2) and was found to be stable.



Scheme 7. Reaction of phenylhydrazine with malononitrile **25**.

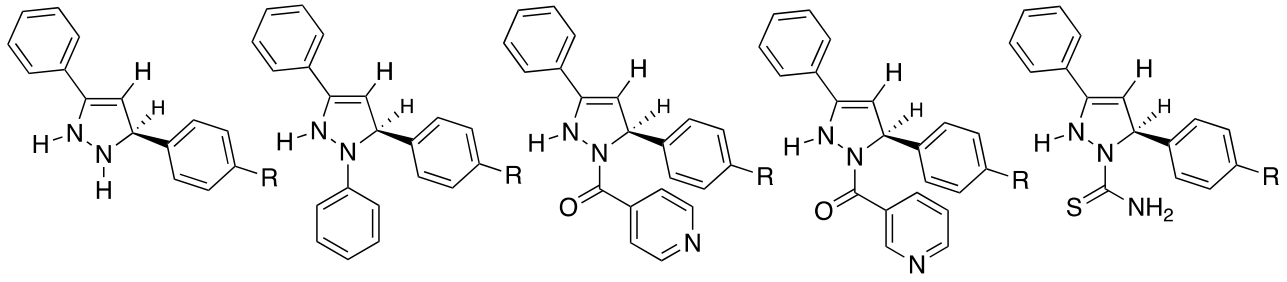
Müller and List reported chiral 3-pyrazolines as intermediates in the synthesis of chiral 2-pyrazolines (Scheme 8).[37,31] A 6π-electrocyclization of protonated α,β-unsaturated hydrazones **27** led to 1-protonated 3-pyrazolines **28**, which isomerized to 2-pyrazolines, with the chirality arising from the use of a chiral Brønsted acid used as catalyst.



27 **28**

Scheme 8. Müller and List mechanism.

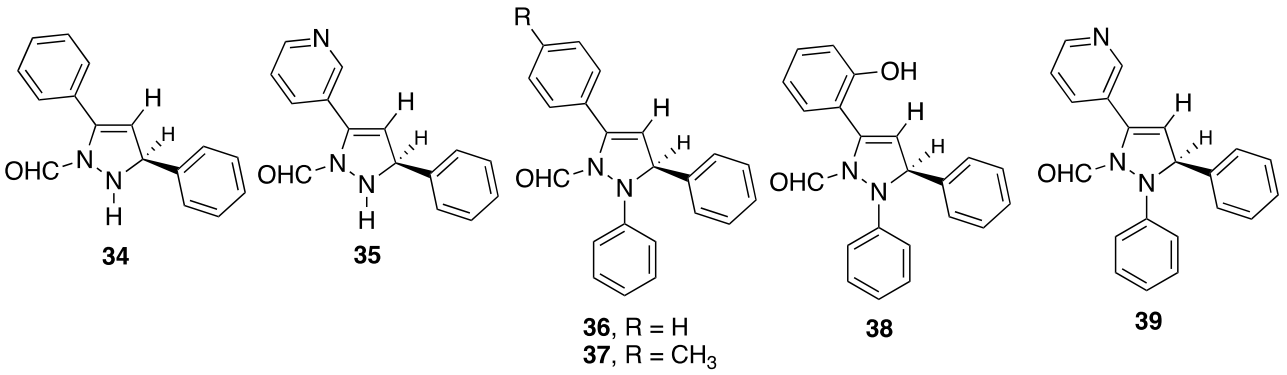
Swarnkar *et al*. reacted chalcones with different hydrazines under microwave irradiation and obtained 3-pyrazolines **29**–**33** (Figure 5).[38] This result is very unexpected and the compounds were characterized by an NH band in the IR spectra and by two (**30**–**33**) or three (**29**) signals in the ^{1}H NMR spectra due to the NH and the saturated CH at position 5. We have tried to repeat this work without success.



29 **30** **31** **32** **33**

Figure 5. Swarnkar's 3-pyrazolines.

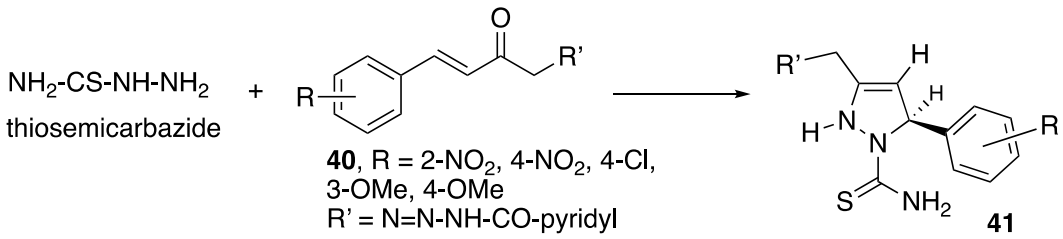
Jetti *et al*. followed an approach related to previous work but isolated the intermediate NH-3-pyrazolines in the form of 2-formyl derivatives prior to obtaining 1-formyl-2*H*-3-pyrazolines **34** and **35** and 1-formyl-2R-3-pyrazolines **36**, **37**, **38** and **39** (Figure 6).[39] These structures warrant further exploration.



34 **35** **36**, R = H **37**, R = CH_3 **38** **39**

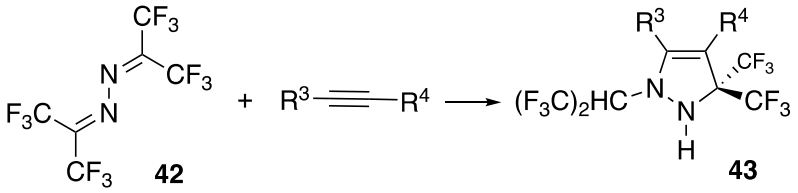
Figure 6. Jetti's 3-pyrazolines.

Kasabe *et al*. reacted thiosemicarbazide with rather unusual β-unsaturated ketones **40** (Scheme 9).[40] The resulting pyrazolines **41** were characterized by IR and ^{1}H NMR spectroscopy but the position of the double bond remained ambiguous.



Scheme 9. Kasabe's 3-pyrazolines.

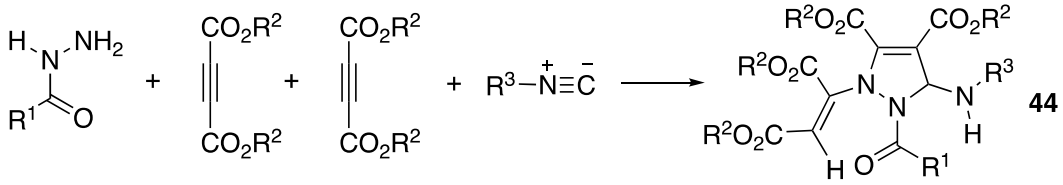
Burger *et al*. obtained 3-pyrazolines **43** by a *criss-cross* cycloaddition in which hexafluoroacetone azine **42** was reacted with acetylenes (Scheme 10).[41,42] Pyrazolines **43** provide another example of compounds like **8** in Scheme 2. In this work we have included [(NNC + CC)] at this point because hexafluoroacetone azine **42** is obtained from hexafluoroacetone and hydrazine. We have included this work in the [(NNC + CC)] section because hexafluoroacetone azine **42** is obtained from hexafluoroacetone and hydrazine.



Scheme 10. Burger's 3-pyrazolines.

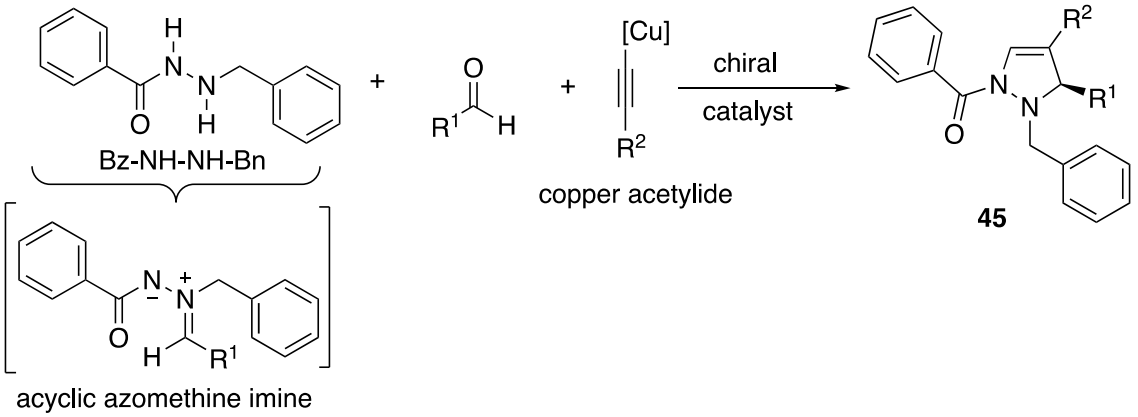
2.1.2. Hydrazides. The method involving hydrazides has been widely used, especially with phthalazine as the starting material. The presence of acyl substituents leads to a considerable decrease in the basicity of hydrazines and stabilizes 3-pyrazolines.

2.1.2.1. Monosubstituted hydrazides. A four-component reaction involving hydrazides, two acetylenic diesters and isocyanides affords highly substituted 3-pyrazolines **44** (Scheme 11).[43]



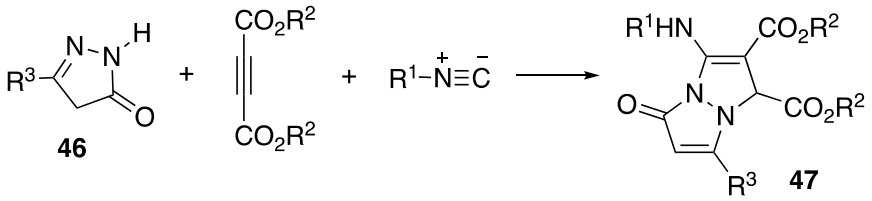
Scheme 11. Synthesis of 3-pyrazolines **44** from hydrazides.

As in other branches of chemistry, the natural evolution of synthetic methods is moving towards catalytic asymmetric synthesis. This approach was successfully applied to the synthesis of **45** starting from a monosubstituted hydrazide, *N*'-benzylbenzohydrazide (Scheme 12).[44] As in other synthetic methods, this reaction involves a reagent that is not isolated, namely an acyclic azomethine imine (Section 2.2).



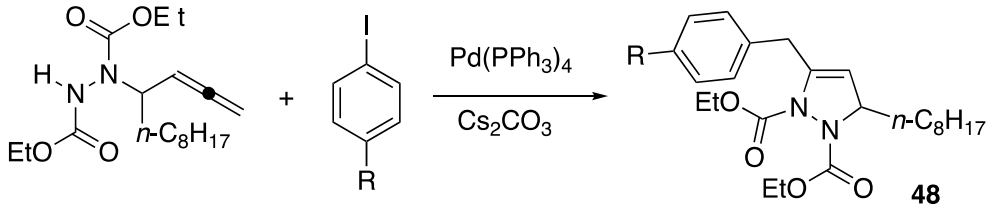
Scheme 12. Enantioselective synthesis of 3-pyrazolines **45**.

1*H*-Pyrazolin-5-ones **46** are related to monosubstituted hydrazides in the sense that they behave in a similar way (Scheme 13). The results provided in Scheme 13 represent an interesting way to prepare derivatives of pyrazolo[1,2-*a*]pyrazole **47** by a three-component reaction.[45-47]



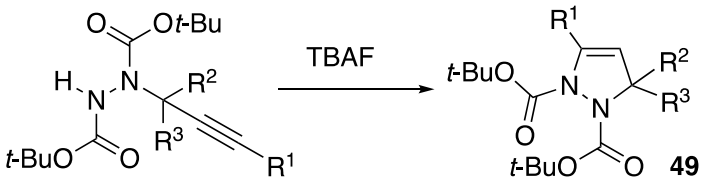
Scheme 13. Multicomponent synthesis of pyrazolo[1,2-*a*]pyrazoles **47** with a 3-pyrazoline structure.

2.1.2.2. Disubstituted hydrazides. Open ring. An efficient synthesis of 3-pyrazolines **48** by a Pd(0)-catalyzed coupling-cyclization reaction between 2-substituted 2,3-allenylhydrazides and aryl iodides was described by Ma;[48] the reaction product (Scheme 14) was accompanied by small amounts of 1,2-diazetidines.



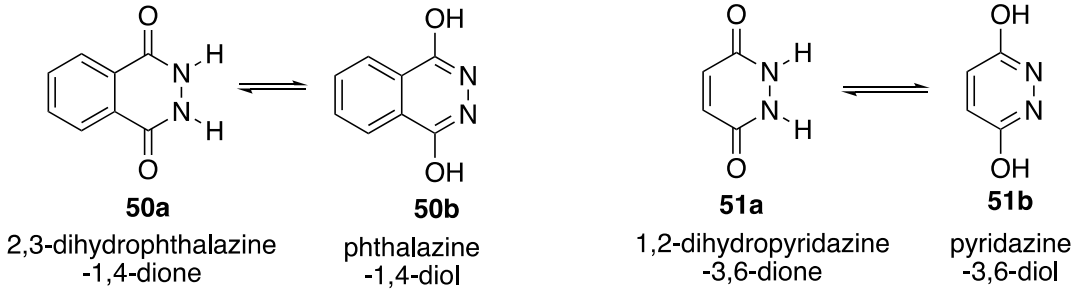
Scheme 14. Synthesis of 3-pyrazolines **48** from 2-substituted 2,3-allenylhydrazides.

The intramolecular cyclization of 1,2-Boc-substituted hydrazines bearing an alkyne substituent affords 3-pyrazolines **49** (Scheme 15); the reaction scope has been extended to include enantioselective synthesis using a chiral phosphoric acid catalyst.[49]



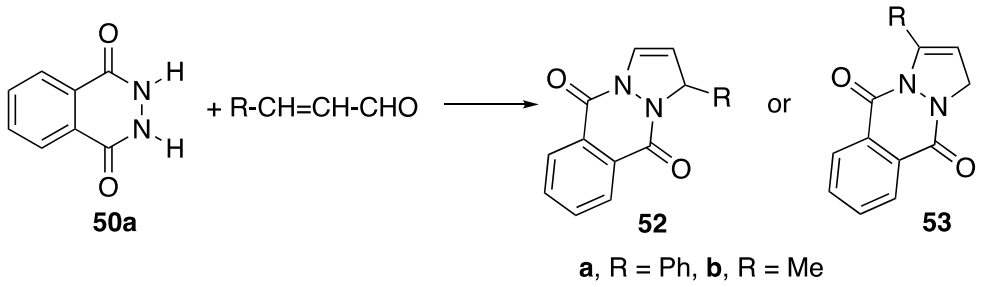
Scheme 15. Intramolecular cyclization of 1,2-Boc-substituted hydrazines.

2.1.2.3. Disubstituted hydrazides. Cyclic. This method is one of the most widely used [(NN) + (C) + (CC)] or [(NN) + (CCC)] pathways to 3-pyrazolines; the stability of hydrazides, the easy crystallization of aromatic compounds, and the accessibility of 2,3-dihydrophthalazine-1,4-diones all contribute to the success of this method (see Scheme 16). Although dione **50a** is clearly the major tautomer (Scheme 16), some authors represent this compound as phthalazine-1,4-diol **50b**, but this is irrelevant in terms of the reactivity. There are very few papers in which the use of the simplified derivative **51** (same problem with their tautomerism) has been reported.[50]



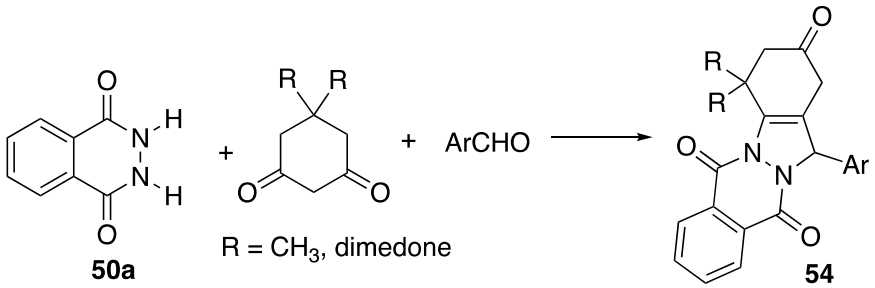
Scheme 16. Cyclic disubstituted hydrazides.

Discovered by Drew and Hatt in 1937 (R = Ph),[51] this is the oldest method for the synthesis of 3-pyrazolines, although the position of the double bond, **52a** or **53a**, was not determined (Scheme 17). The correct structures **52a** and **52b** were established by Le Berre and Godin.[52,53] These works were discussed by Tisler and Stanovnik in Chapter III 'Azolo- and Azinopyridazines and Some Oxa and Thia Analogs' in Castle`s book.[54]



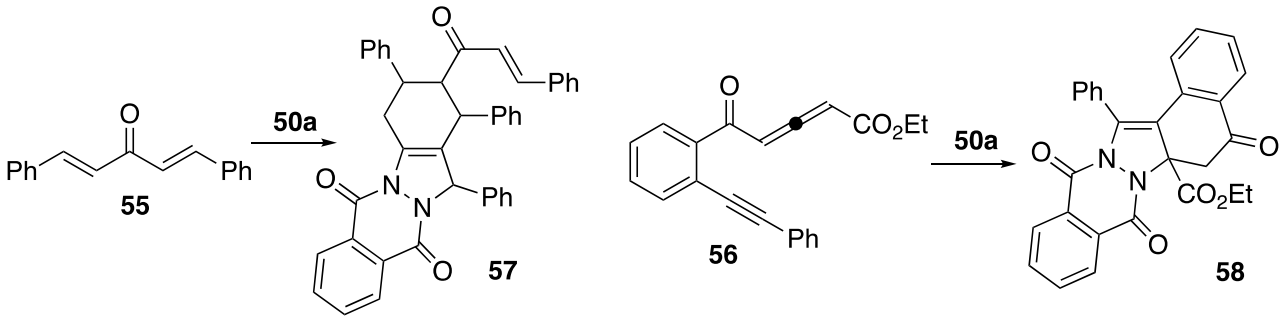
Scheme 17. Drew and Hatt synthesis.

The most commonly reported example is represented in Scheme 18.[55-62] The X-ray structures of several 3-pyrazolines with structure **54**, prepared by this method, have been determined.[63,64]



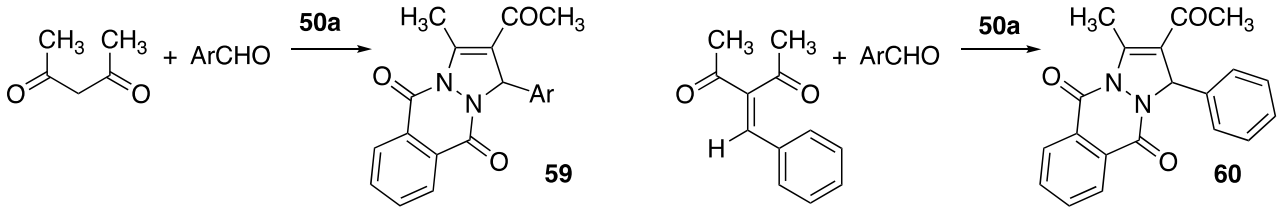
Scheme 18. Synthesis of 3-pyrazolines **54** from 2,3-dihydrophthalazine-1,4-dione **50a**.

Other β-unsaturated carbonyl compounds such as **55** and **56** afford more complex 3-pyrazolines, e.g., **57** and **58**, respectively, upon reaction with **50a** (Scheme 19).[65,66]



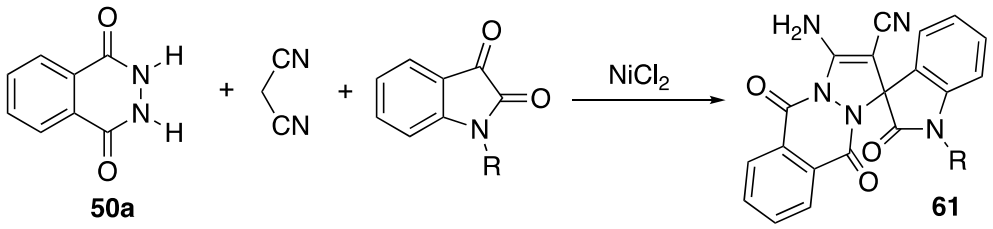
Scheme 19. Polycyclic 3-pyrazolines **57** and **58**.

Open-ring β-diketones such as acetylacetone have rarely been used (Scheme 20) but this compound affords 3-pyrazolines **59** and **60**. β-Ketoesters (ethyl acetoacetate), benzaldehyde and 1,3,5-triazolidine-3,5-dione (another cyclic hydrazide) have also been used to prepare 3-pyrazolines.[67]



Scheme 20. Reaction of 2,3-dihydrophthalazine-1,4-dione **50a** with β-diketones and aromatic aldehydes.

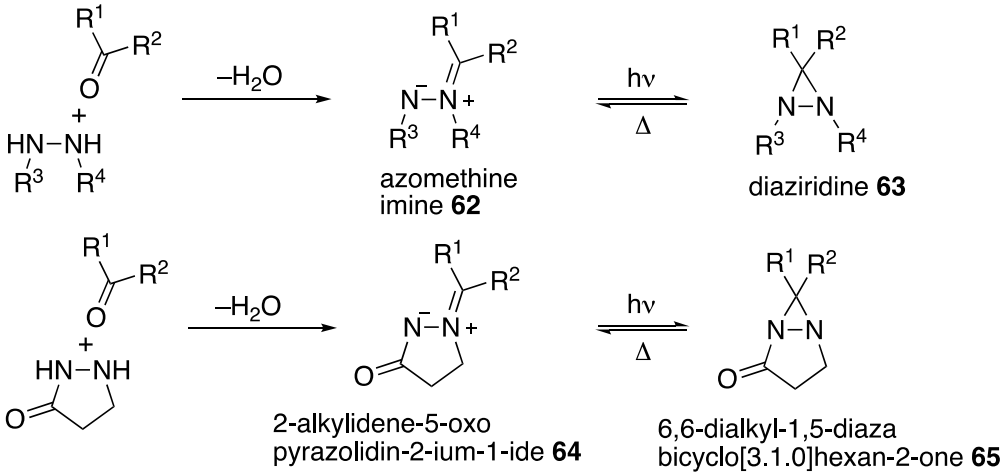
A less commonly used approach involves the use of malononitrile instead of a β-dicarbonyl compound and isatin or *N*-alkyl isatins instead of aromatic aldehydes (Scheme 21) to form spirooxindoles **61**.[59,68-70]



Scheme 21. Reaction of 2,3-dihydrophthalazine-1,4-dione **50a** with malononitrile and isatins.

2.2. By 1,3-dipolar cycloaddition [(NNC) + (CC)]

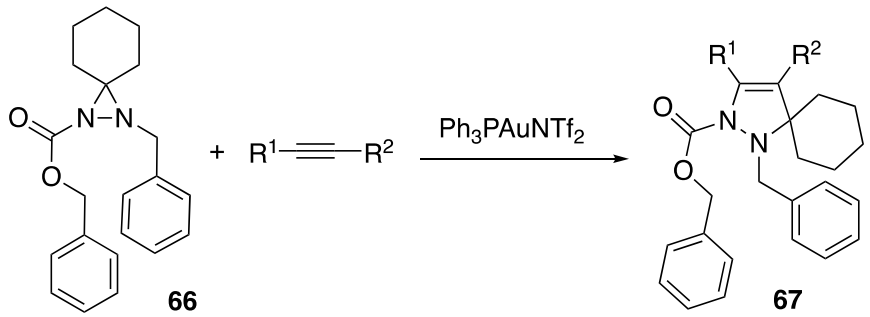
For ease of classification we have separated the two main synthetic methods into 'from hydrazines [(NN) + (C) + (CC) and (NN) + (CCC)]' and 'by 1,3-dipolar cycloadditions [(NNC) + (CC)]' but these methods are closely related (Scheme 22).



Scheme 22. Relationships between different synthetic methods.

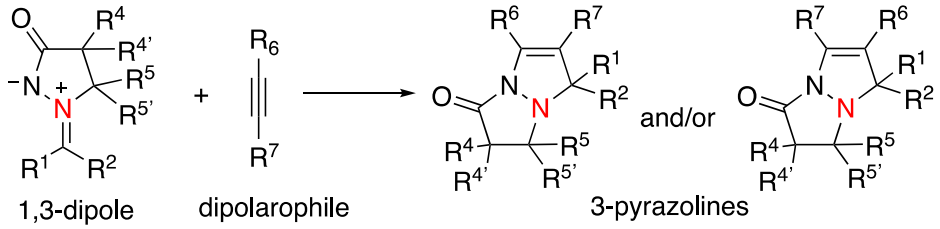
The relationship between azomethine imines, **62** and **64**, and diaziridines, **63** and **65**, was reported by Huisgen in 1961;[71,72] since diaziridines open thermally to 1,3-dipoles, they can be used to prepare 3-pyrazolines[73] (for a review, see references[74,75]). Several authors have studied the **64**/**65** relationship in Scheme 22 between pyrazolidinones and diazabicyclohexanones.[76,77]

2.2.1. Diaziridines as azomethine imine precursors. A remarkable example of a gold(I)-catalyzed synthesis of 3-pyrazolines **67** by reaction of diaziridines **66** and alkynes is shown in Scheme 23.[78]



Scheme 23. Synthesis of 3-pyrazolines **67** from diaziridines **66**.

2.2.2. 2-(Propan-2-ylidene)pyrazolidin-2-ium-1-ides. The general 1,3-dipolar cycloaddition between 2-(propan-2-ylidene)pyrazolidin-2-ium-1-ides and CC triple bonds (or allenes) to afford 3-pyrazolines is represented in Scheme 24. The latter compounds are related to the pyrazolo[1,2-*a*]pyrazole ring system and two regioisomers can be formed depending on the nature of R^6 and R^7.



Scheme 24. General synthesis of 3-pyrazolines from 2-(propan-2-ylidene)pyrazolidin-2-ium-1-ides.

The most relevant 1,3-dipoles, **68**–**78**, are summarized in Figure 7 and the most frequently used dipolarophiles, **79**–**91**, are shown in Figure 8.

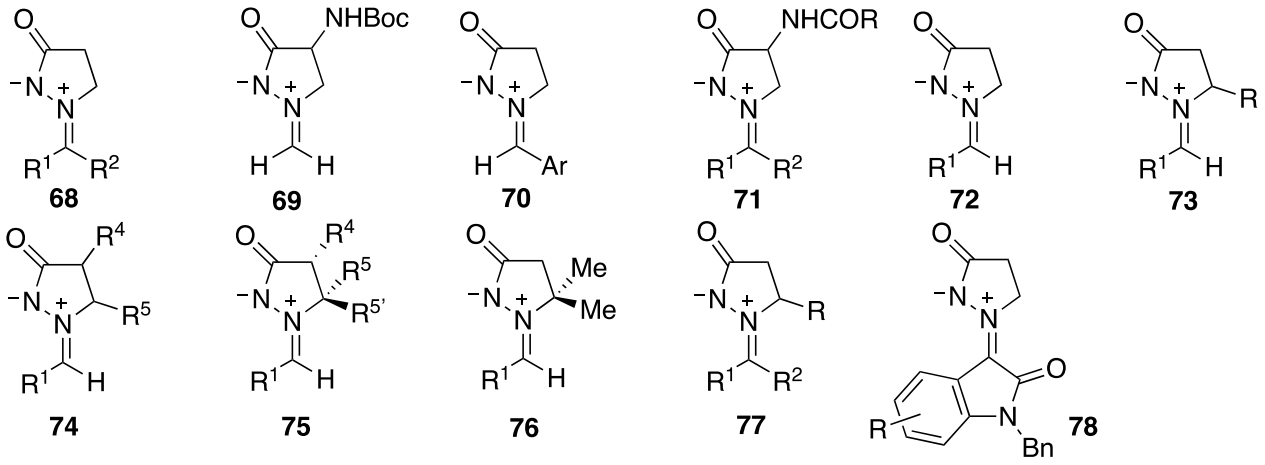


Figure 7. 2-(Propan-2-ylidene)pyrazolidin-2-ium-1-ides.

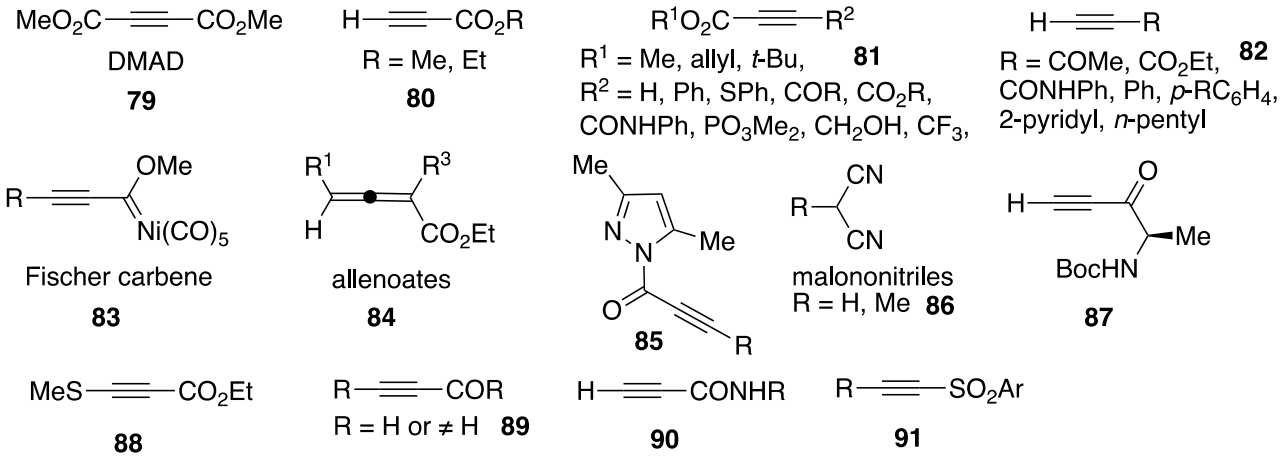


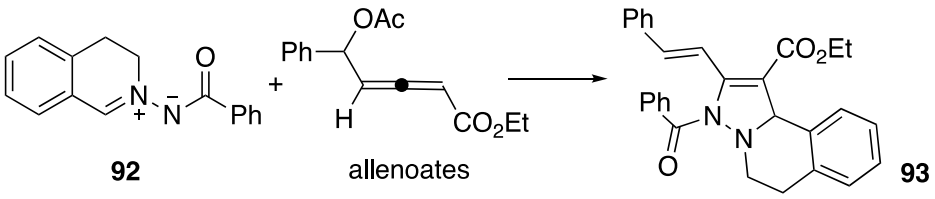
Figure 8. Alkene, allene, alkyne and nitrile dipolarophiles.

Table 1 contains the references corresponding to the combinations of the compounds shown in Figures 7 and 8.

Table 1. 1,3-Dipolar cycloadditions

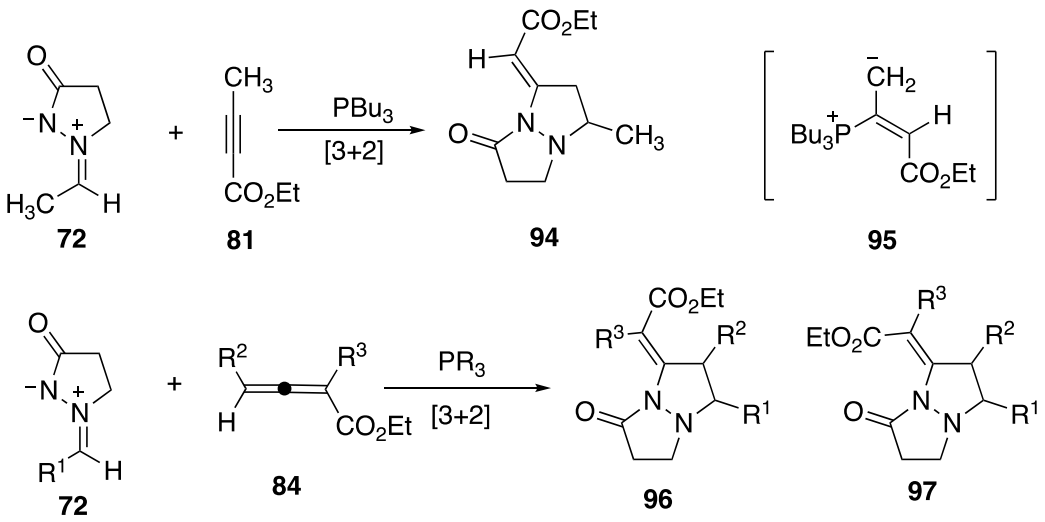
1,3-Dipole	Dipolarophile	Comments	Reference
68	**79**		79
68	**79**, **82**, **89**, **91**		80
69	**81**		81,82
70	**79**, **80**		83
71	**79**		84
72	**82**		85
72	**82**	Catalyzed by metal amides	86
72	**80**, **89**		87
72	**80**	Catalyzed by Cu(I), asymmetric	88
72	**84**	DMAD	89
72	**85**		90
72	**86**		91
72	**89**	Using MW	92
73	**82**	Kinetic resolution	93
74	**83**	Regioselective	94
74	**87**	Absolute configuration	95
75	**87**	Absolute configuration	96
75	**89**	Allenoates	96
75	**89**	Allenoates, catalyzed by Cu(0)	97
75	**90**	Catalyzed by Cu(0)	98
76	**89**		88
76	**91**	Malononitriles	88
76	**80**	Catalyzed by Cu(I)	98
76	**88**	Fischer carbene	99
77	**90**		99
78	**80**		100

An example of a reaction between an azomethine imine **92** and an allene derivative to afford the 3-pyrazoline **93** is presented in Scheme 25.[97,101]



Scheme 25. Synthesis of 3-pyrazoline **93** from azomethine imine **92**.

When the reaction of 2-(propan-2-ylidene)pyrazolidin-2-ium-1-ides and triple bonds or allenes was catalyzed by a phosphine, the reaction followed a different mechanism and 3-methylene-pyrazolidines were obtained (Scheme 26).



Scheme 26. [3+2] Dipolar cycloadditions catalyzed by phosphines.

Compound **94** was obtained from the acetylenic ester **81** (structure **95** was proposed as an intermediate),[102] while a mixture of *E* and Z isomers, **96** and **97**, was obtained from allenoate **84**.[103] If the allenoate has R^2 = H, then the reaction only gives the *E* isomer **96** (in this paper the mechanism was analyzed in detail).[104] The structure of **97** (R^1 = *p*-NO_2-C_6H_4, R^2 = R^3 = H, Refcode UZIRUR) was determined by X-ray crystallography (Figure 9).

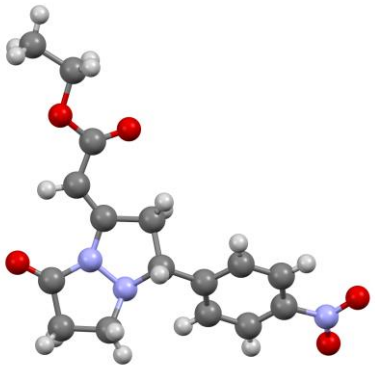
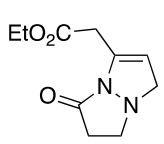
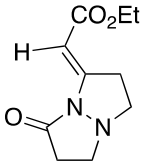
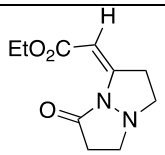
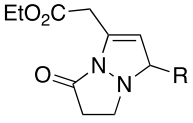
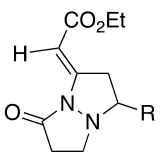
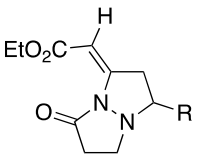


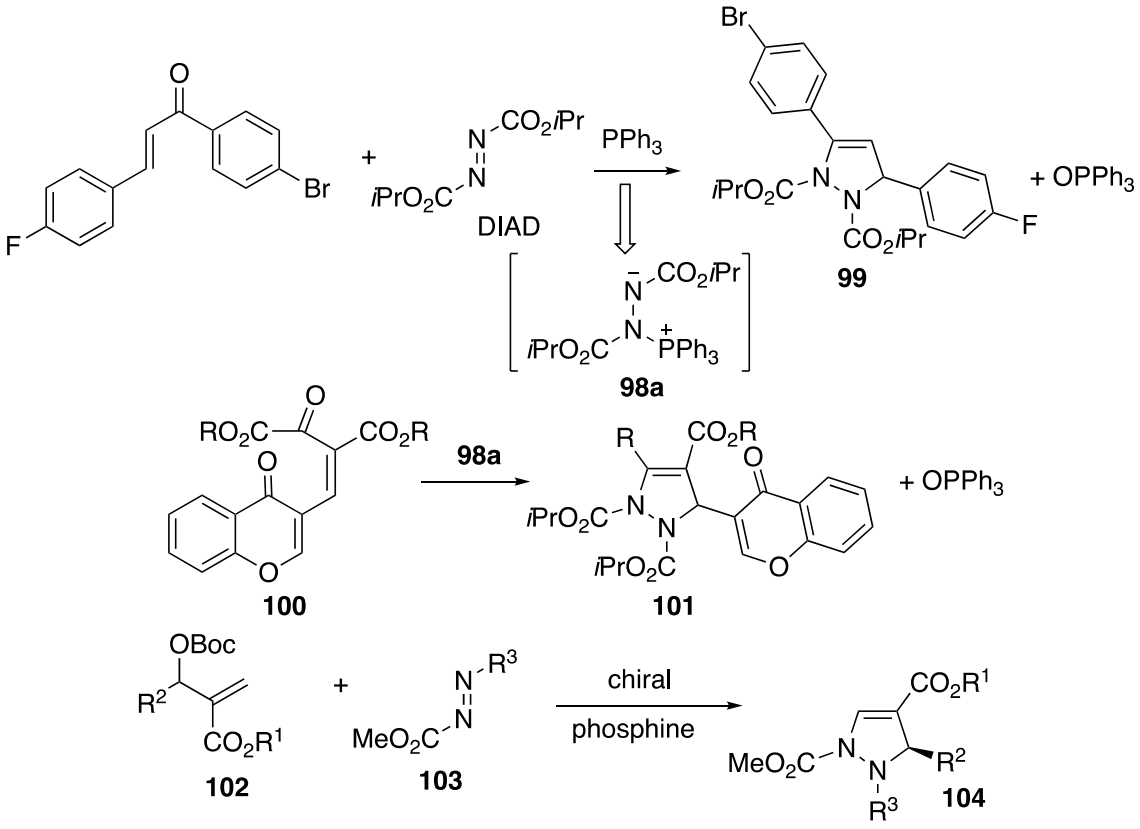
Figure 9. The structure of UZIRUR.

Compounds **96** and **97** present tautomerism of the *endo*/*exo* class (Section 3.2) with two *exo*-isomers that we calculated (Table 2) at the B3LYP/6-311++G(d,p) level. The calculations reproduce the experimental evidence.

Table 2. Position of the CC double bond in compounds **96** and **97**. Relative energies in kJ·mol^{-1}

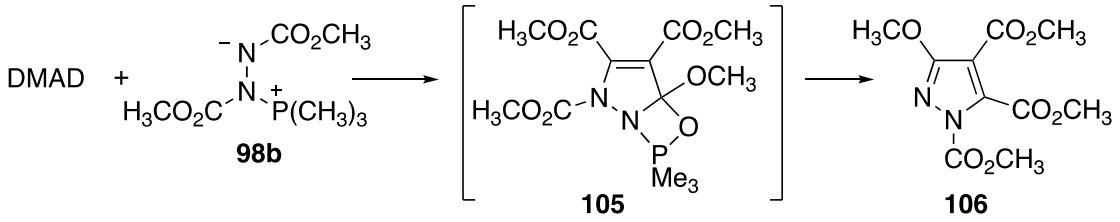
	Model compound			Real compound, R = *p*-$NO_2C_6H_4$		
	endo	*exo-E*	*exo-Z*	*endo*	*exo-E*	*exo-Z*
						
E_{rel}	40.9	0.0	45.6	36.9	0.0: UZIRUR	46.2

2.2.3. Diethyl azodicarboxylate and the Morrison–Brunn–Huisgen betaine. Diethyl azodicarboxylate reacts with phosphines to afford the Morrison–Brunn–Huisgen betaines (**98**),[105,106] a 1,3-dipole that constitutes the first step of the Mitsunobu reaction.[107] The synthesis of a diisopropyl 3-pyrazoline-1,2-dicarboxylate **99** was carried out by this method from a halogenated chalcone and DIAD (Scheme 27). Compound **98a** was not isolated.[108] The difficult problem of assigning the bromo- and fluorophenyl groups of compound **99** at the 3- and 5-positions, respectively, was solved by X-ray crystallography (Section 4.6). Two more examples are represented in Scheme 27, one involving the same betaine **98a** and chromone **100** to prepare **101**[109] and the other a chiral betaine related to **103** and a vinyl ester **102** to prepare the chiral 3-pyrazoline **104**.[110]



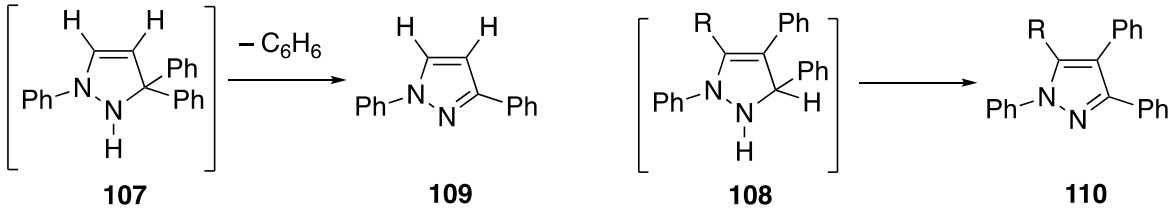
Scheme 27. The use of Morrison–Brunn–Huisgen betaines.

Another example is presented in Scheme 28 and in this case 3-pyrazoline **105** was postulated as an intermediate to pyrazole **106**.[111]



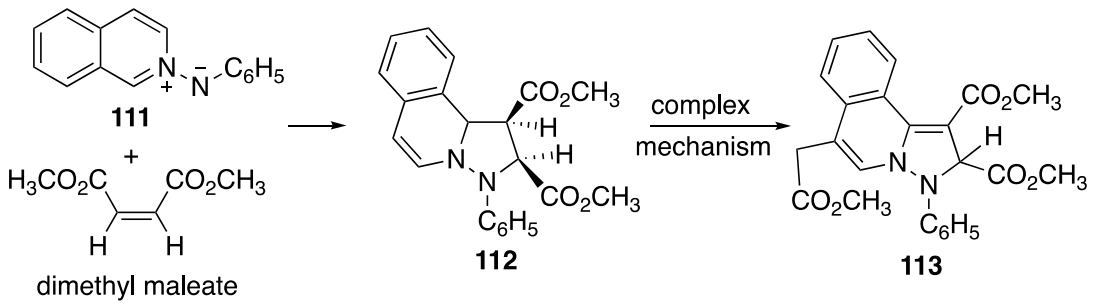
Scheme 28. Another use of the Morrison–Brunn–Huisgen betaines.

2.2.4. From sydnones and other 1,3-dipoles. In the synthesis of pyrazoles from sydnones and olefins, 1*H*-2-phenyl-3-pyrazolines **107** and **108** have been postulated as intermediates in the synthesis of pyrazoles **109** and **110** (Scheme 29).[112]



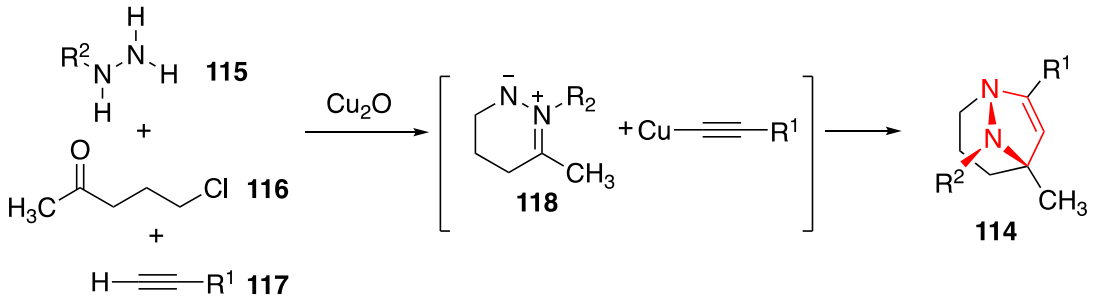
Scheme 29. Synthesis of pyrazoles **110** from sydnones.

A very complex mechanism was proposed to explain the formation of 3-pyrazoline **113**, the structure of which was determined by X-ray crystallography in 1985.[113] A further fifteen years passed before the mechanism was published for the transformation of pyrazolidine **112**, obtained from the dipole **111** and dimethyl maleate, into the 3-pyrazoline **113** with an unexpected supplementary $CH_2CO_2CH_3$ arm (Scheme 30).[114,115]



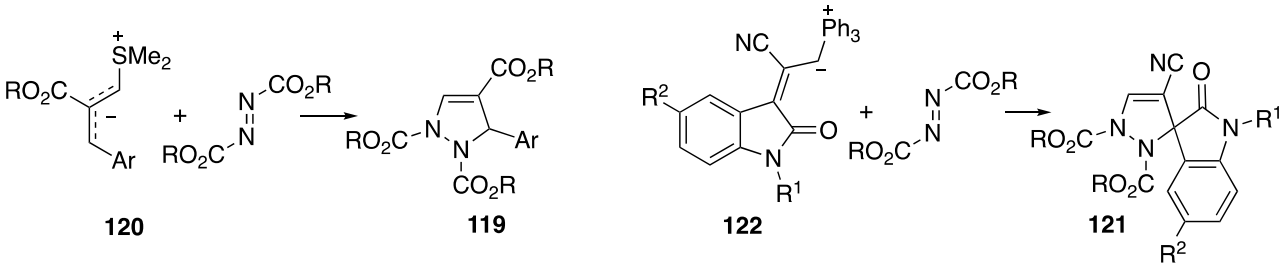
Scheme 30. Synthesis of 3-pyrazoline **113**.

One of the most curious 3-pyrazolines synthesized was part of a 1-aza-6,7-dehydrotropane skeleton **114**. The synthesis, a one pot three-component reaction, starts from monosubstituted hydrazine **115**, 5-chloropentan-2-one **116** and a terminal alkyne **117** in the presence of Cu_2O (Scheme 31). The azomethine imine intermediate **118** was not isolated.[116]



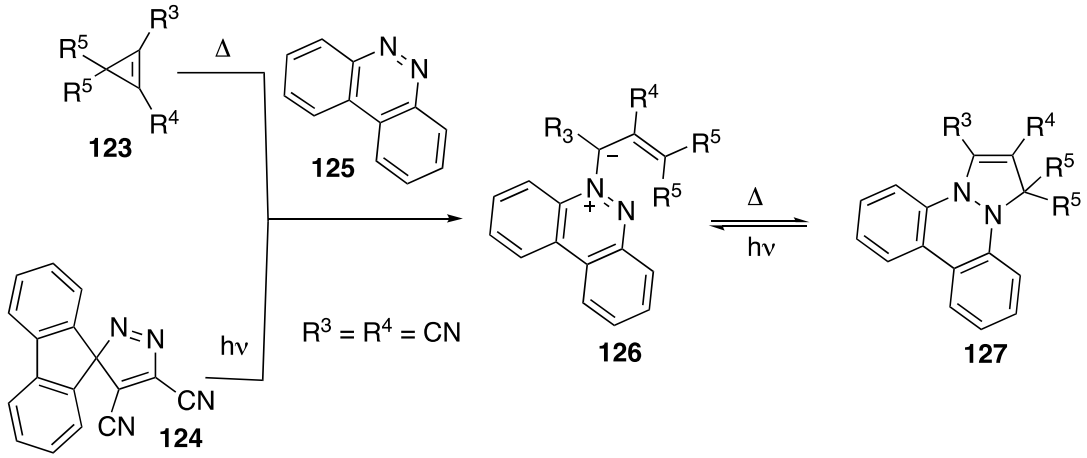
Scheme 31. A 3-pyrazoline with an azadehydrotropane structure.

Another way to prepare 3-pyrazolines by an [(NN) + (CCC)] approach that it is very different from the methods based on hydrazines (Section 2.1) is to use a [3+2] cycloaddition but with the dipole on the (CCC) fragment, which is related to the Baylis–Hillman bromide, and the dipolarophile is an azo derivative such as diethyl azodicarboxylate (Scheme 32, R = Et). The synthesis of 3-pyrazoline **119** from the dipole **120** was described in reference[117] and the more complex case in which **121** is obtained from **122** (Morita–Baylis–Hillman adducts) in reference.[118]



Scheme 32. The use of (CCC) 1,3-dipoles.

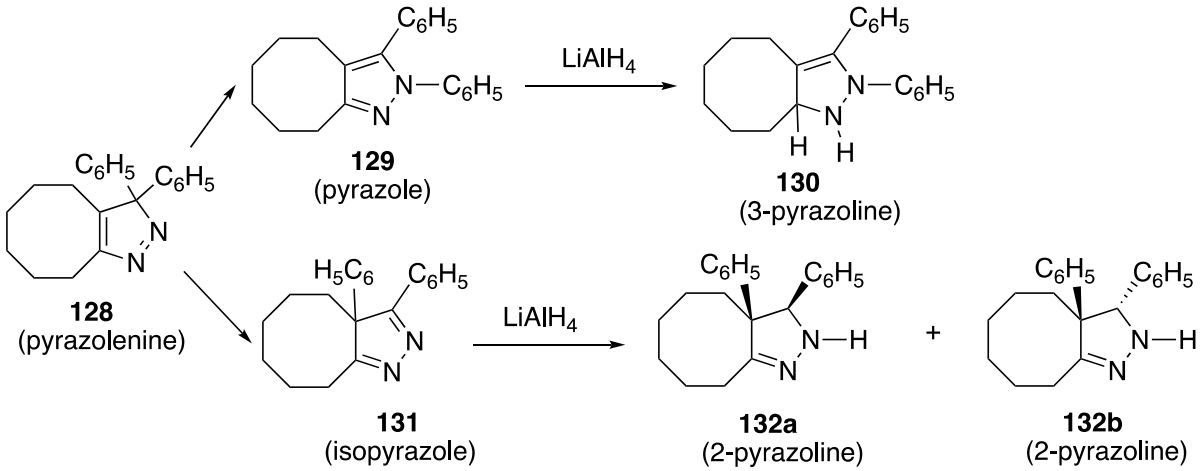
2.2.5. 1,5-Electrocyclic reactions. A rare and beautiful example of a 1,5-electrocyclic reaction was reported by Dürr *et al*. (Scheme 33).[119] Starting with a thermal reaction of cyclopropene **123** or photochemical reaction of pyrazolenine **124** and benzo[*c*]cinnoline **125**, the azomethine imine **126** and the 3-pyrazoline **127** were isolated and rearranged. The photochemical ring opening of **127** to **126** is a property that will be discussed in Section 3.9.



Scheme 33. Synthesis of 1*H*-benzo[*c*]pyrazolo[1,2-*a*]cinnolines **127**.

2.3. Other methods

2.3.1. By reduction of pyrazoles, pyrazolones and pyrazolidinones. Reduction of pyrazoles to 3-pyrazolines is not expected to work well because this will lead to 1-R-2*H*-3-pyrazolines, which would usually isomerize to 2-pyrazolines (see Section 3.2). Moreover, pyrazoles are resistant to reduction, in particular by lithium aluminium hydride.[120] The only example of this process was reported by Wittig and Hutchison (Scheme 34), who claimed to have isolated 3-pyrazoline **130** by reduction of pyrazole **129**.[121] This claim was later proved to be incorrect[122] due to an indirect error that affects the structure of pyrazole **129**. When the reaction was repeated, the rearrangement of the pyrazolenine **128** did not afford pyrazole **129** but isopyrazole **131**; the reduction of **131** afforded two isomeric 2-pyrazolines, the major *cis* isomer **132a** with identical properties to those reported for **130** and the minor isomer *trans* **132b**.

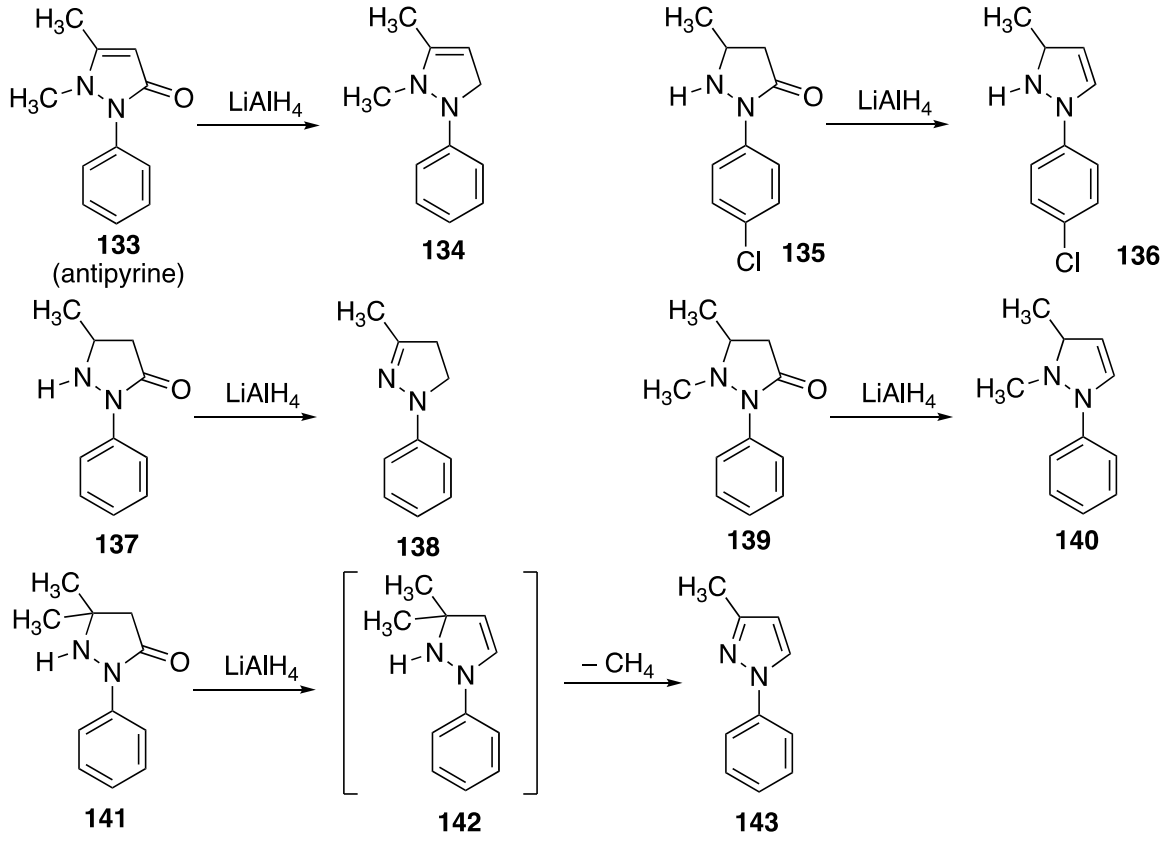


Scheme 34. The Wittig and Hutchison synthesis.[122]

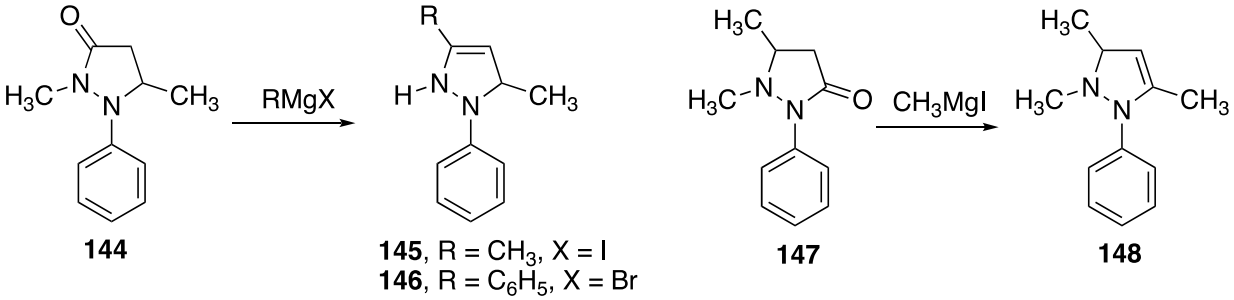
Concerning pyrazolones (Scheme 35), in 1957 Bowman and Franklin reported the reduction of antipyrine (**133**) to the 3-pyrazoline **134**[123] and in 1963 Wagner-Jauregg and Zirngibl described the reduction of pyrazolidinone **135** to 4-pyrazoline **136**.[124] The instability of these tautomers and their easy transformation into 2-pyrazolines (Section 3.2) prompted us to study this reaction in 1966 using *N*-phenyl **137** instead of *N*-*p*-chlorophenyl **135** and it was discovered that the reduction product was the 1-phenyl-2-pyrazoline **138**.[125] The original authors acknowledged their error in a subsequent paper.[126]

We also reported the reductions of **139** to **140** and **141** to **143**.[126] Bird reported that compound **141** cannot be reduced by $LiAlH_4$;[127] in fact treatment with $LiAlH_4$ affords 1-phenyl-3-methyl-1*H*-pyrazole **143** by a mechanism that involves a 4-pyrazoline **142**.[126]

An obvious extension of reductions was the use of Grignard reagents (Scheme 36). This approach enabled us to obtain 3-pyrazolines **145** and **146** from pyrazolidinone **144** and 3-pyrazoline **148** from **147**.[128]



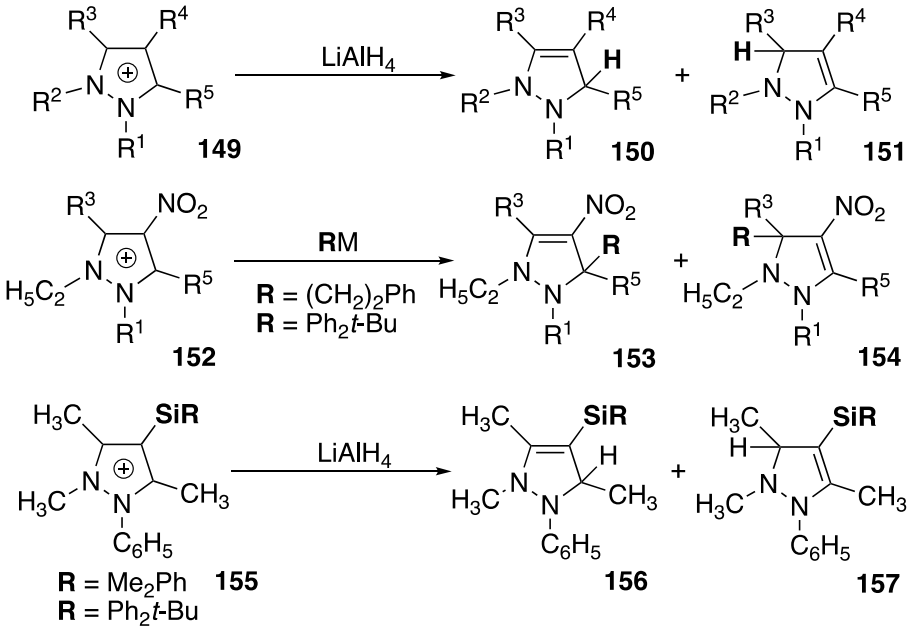
Scheme 35. Reduction of pyrazolones and pyrazolinones.



Scheme 36. The action of Grignard reagents on pyrazolidinones.

2.3.2. By reduction of pyrazolium salts. Discovered in Montpellier (France) and St. Petersburg (Russia) between 1967 and 1973 and developed in Valladolid (Spain) between 1989 and 2009, this is a general and versatile synthetic method, although pyrazolidines are often accompanied by 3-pyrazolines. El'tsov *et al*. reported the same reaction in 1968[129] and they extended it to polarographic reduction.[130] The main problem with this method is that in some cases it yields mixtures of 3-pyrazolines **150** and 4-pyrazolines **151** if the substituents at N1/N2 or C3/C5 of the pyrazolium salt **149** are not sufficiently different (Scheme 37).[131] The first study, in which the substituents were H, CH_3 and C_6H_5, was extended to include many other substituents in a subsequent paper that included kinetic studies and deuterium labeling experiments.[121] In this paper the Grignard reaction was also studied. The attack at positions 3 and 5 depends on the nature of R^3 and R^5. For example, when R^3 = Ph and R^5

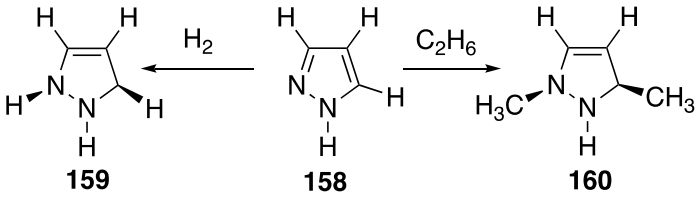
= Me the attack occurs on the C5 (> 95%, < 5%) but a primary isotope effect lowered the percentages to 90% and 10% when $LiAlD_4$ was used.[132]



Scheme 37. Reduction of pyrazolium salts.

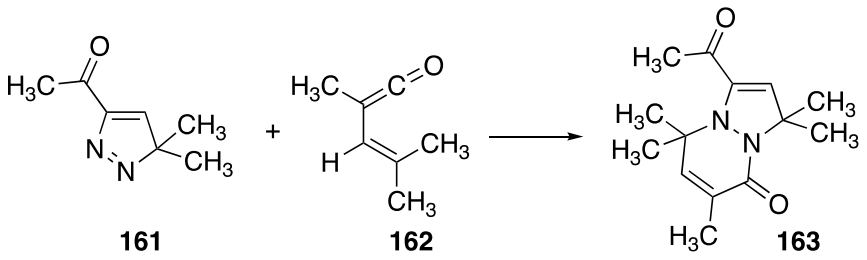
The series of Valladolid papers started with a brief communication concerning simple pyrazolium salts,[133] followed by a paper on the treatment of 4-nitropyrazolium salts **152** with organometallic reagents (CH_3Li, C_6H_5Li, CH_3MgI, C_6H_5MgBr) to afford 3-pyrazolines **153** and **154** (Scheme 37).[134] A subsequent study was performed on the reactivity of pyrazolium salts **155** towards complex metal hydrides to obtain mixtures of 3-pyrazolines **156** and **157**.[135,136] Compounds **156** and **157** are in equilibrium, with **157** being the most stable because, according to the authors, the C4C5 double bond is conjugated with the *N*-phenyl group (see Scheme 43 in Section 3.2).[137] The case where the SiR groups are at position 5 instead of 4 was also studied.[138]

2.3.3. From other pyrazole derivatives. Jursic theoretically calculated hypothetical reactions (Scheme 38) that transform pyrazole **158** into 3-pyrazolines **159** and **160**.[138]



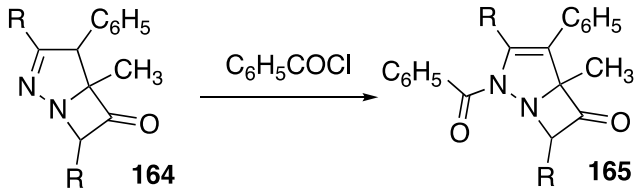
Scheme 38. Theoretical study of relationships between pyrazoles and 3-pyrazolines.

Pyrazolenines (3*H*-pyrazoles) are cyclic azo compounds. Thus, 1-(3,3-dimethyl-3*H*-pyrazol-5-yl)ethan-1-one (**161**) reacts with 2,4-dimethylpenta-1,3-dien-1-one (**162**, a vinylketene) to yield the pyrazolo[1,2-*a*]pyridazinone **163** by a [4+2] cycloaddition (Scheme 39).[139]



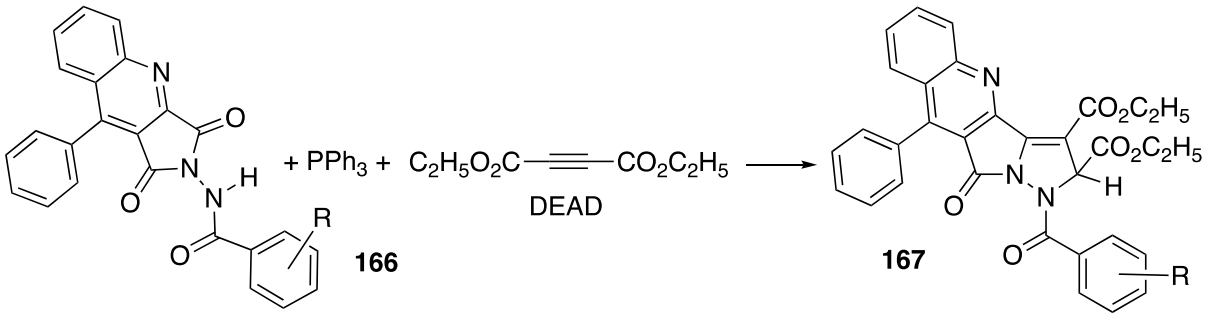
Scheme 39. 3-Pyrazoline **163** from pyrazolenines.

There is a rare example (Scheme 40) of a 3-pyrazoline (**165**) that was obtained by acylation of a 2-pyrazoline **164**.[140]



Scheme 40. Benzoylation of 2-pyrazoline **164**.

2.3.4. Non-conventional methods. Some methods are difficult to classify and these include the reaction represented in Scheme 41, where a disubstituted open hydrazide **166** reacts with DEAD in the presence of triphenylphosphine to afford the polycyclic 1,2-diacyl-3-pyrazoline **167**.[141]



Scheme 41. Synthesis of the polycyclic 3-pyrazoline **167**.

The position of the double bond in **167** (R = *p*-Cl) was established by X-ray crystallography (Figure 10, Refcode: ZEWBAH).[141]

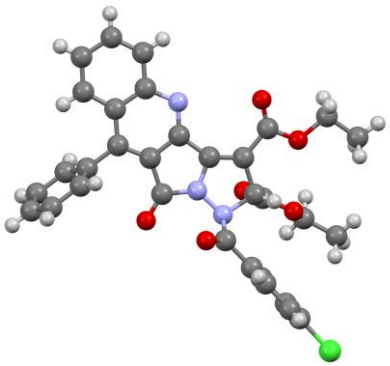


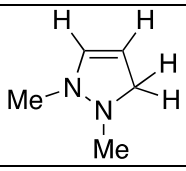
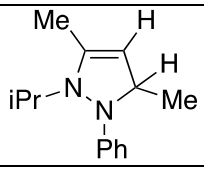
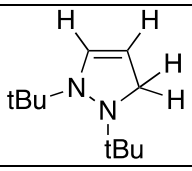
Figure 10. The structure of ZEWBAH.

3. Chemical Properties

3.1. Conformational analysis

In 3-pyrazolines the substituents on the nitrogen atoms adopt a *trans* disposition; the *cis* isomer is much less stable to the point that in some cases it is not stable and corresponds to a transition state.[142] When a substituent is present at position 5 (the other being an H atom) the minimum energy conformation corresponds to the *trans-trans* isomer. The experimental barriers to the double nitrogen inversion were measured by Kostyanovsky *et al*. in two cases.[34,35] The results are provided in Table 3 together with those of the theoretical calculations.

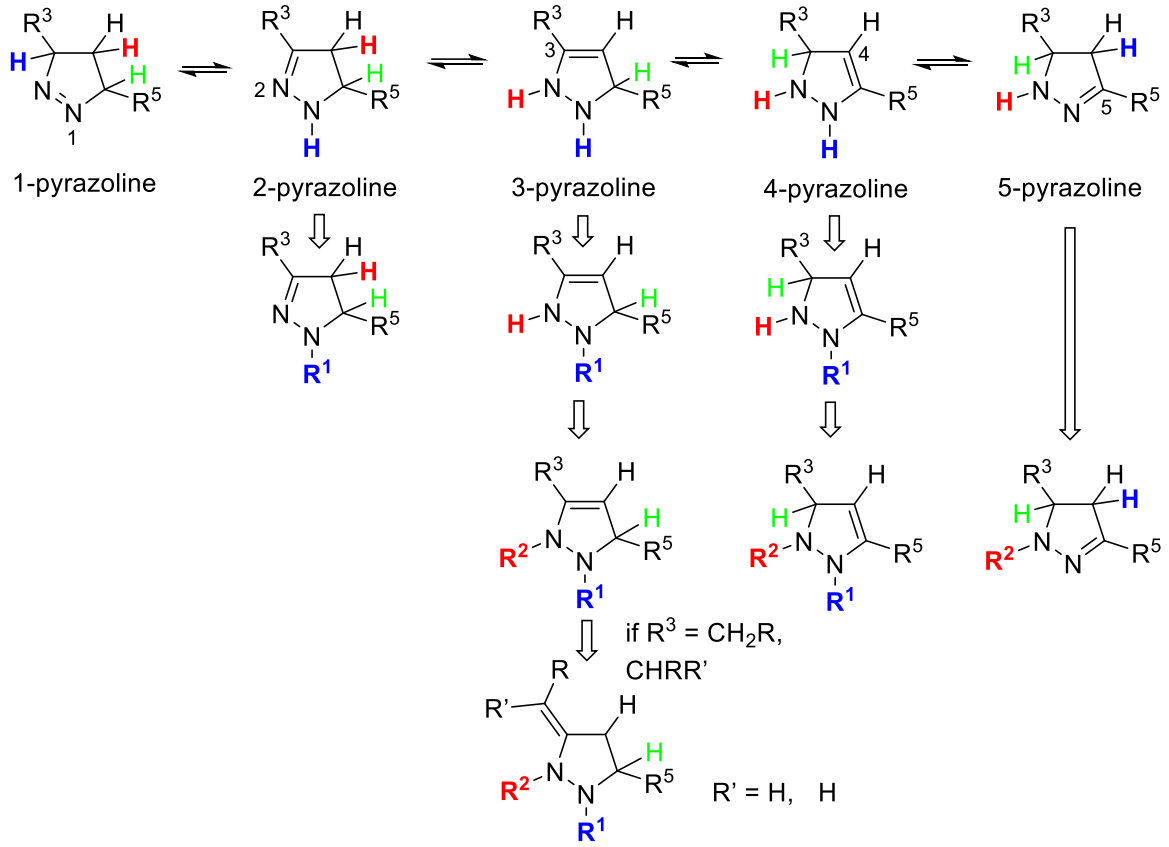
Table 3. Barriers to the N–R inversion (kJ·mol^{-1}) for pyrazolines **168**–**170**

3-Pyrazoline			
	168	**169**	**170**
Calculated	42.7[143]	71.2[143]	125.2[143]
Experimental	Not measured	67.7[34,35]	Blocked[34,35]

The five-membered ring, as in cyclopentene, has an envelope conformation but the potential curve is very flat.

3.2. Tautomerism and prototropy

Although there are only three classes of pyrazolines, there are five tautomers when $R^3 \neq R^5$ (Scheme 42). When one of the nitrogen atoms is substituted (replace H by R^1) the number of tautomers is reduced to two 3-pyrazolines (replace H with R^2). Finally, if R^3 is an alkyl derivative (CH_3, CH_2R, CHRR') there exists the possibility of an *exo*-methylene tautomer;[15] the presence of this tautomer, which is always minor, and its dependence on the solvent and the temperature were studied.[23]



Scheme 42. The complex problem of the tautomerism of pyrazolines.

This phenomenon is important as far as the cyclic structures are concerned because there are numerous possible open-ring structures that in general are not very probable isomers. In the case of 2-pyrazolines the most stable is the hydrazone.[144]

In the Introduction we discussed the structure of N-(2,2-dichloroacetyl)-3,5,5-trimethyl-pyrazoline-1-carboxamide (YAKYAK) as either 3- (**1**) or 2- (**2**).[10] The energies and optimized geometries of these species were calculated at the B3LYP/6-311++G(d,p) level (Figure 11). The 2-pyrazoline **2** is more stable than the 3-pyrazoline **1** by 75.8 kJ·mol^{-1}. Some geometrical data are reported in Figure 11 and, since there are two independent molecules in the unit cell, the distances of the N1–N2–C3–C4 fragment have been averaged: there is no doubt that the structure of YAKYAK is that of a 2-pyrazoline **2**. It is also worth noting that the conformation of the 2,2-dichloroacetamide group is consistent with the presence of an N–H···N2 hydrogen bond in structure **2**.

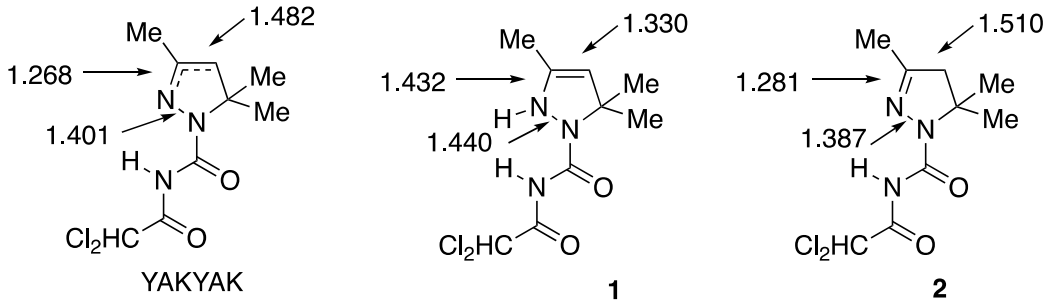
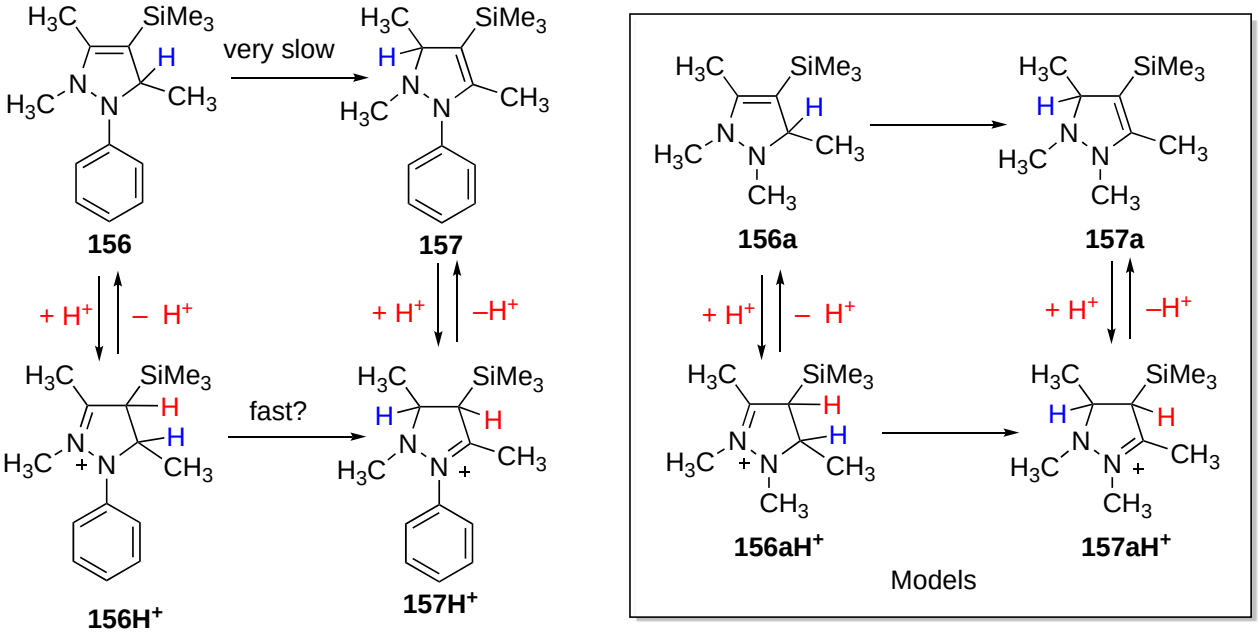


Figure 11. The structure of YAKYAK.

We have already discussed how the isolation of a 2*H*-3-pyrazoline **130** (Scheme 37)[122] was incorrect.[123] Other examples of 2*H*-3-pyrazolines (Schemes 9 and 11)[39,41] were also in doubt.[145]

By far the most interesting result was that reported by González-Nogal *et al*. (Scheme 37).[137] According to these authors, the 3-pyrazoline **156** and the mixture of **156** and **157** were converted to the 3-pyrazoline **157** after several days at room temperature. The 3-pyrazoline **157** is the thermodynamic product because of its greater stability due to the conjugation of the double bond with the *N*-phenyl group. This isomerization was favored by an acidic medium when the experiment was carried out in an aqueous solution of ammonium chloride and probably involved C-protonated cations **H**$^+$ (Scheme 43).

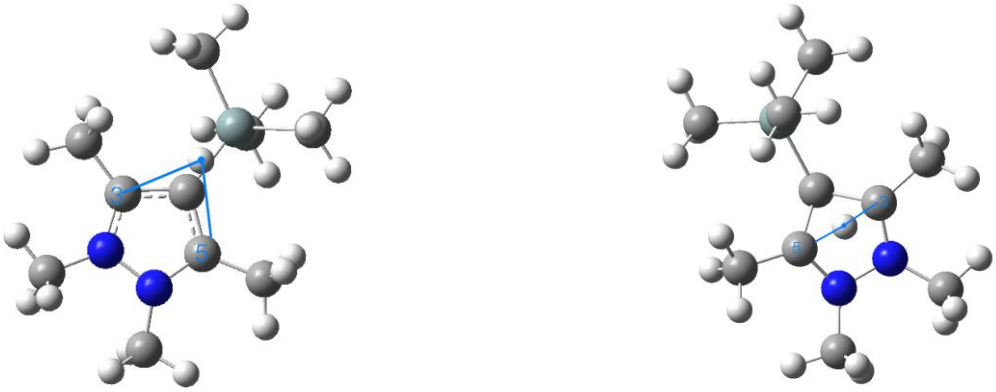


Scheme 43. Δ^3/Δ^4-pyrazoline tautomerism.

We carried out B3LYP/6-311++G(d,p) calculations on the compounds in Scheme 43 and these include model compounds (series **a**) in which the *N*-phenyl ring has been replaced by an *N*-methyl group. According to the calculations **157** is less stable than **156** by 31.0 kJ·mol^{-1}. The barriers of the C5H to C3H proton transfer were calculated on the model compounds. In these compounds the initial and final compounds are the same (autotrope or degenerate tautomerism), *i.e.*, **156a** ≡ **157a** and **156aH**$^+$ ≡ **157aH**$^+$, and this facilitates the location of the transition states (TSs). The calculated barriers are 313 and 236 kJ·mol^{-1}, respectively, and these very high barriers are expected since they correspond to thermally forbidden [1,3] sigmatropic shifts (Figure 12).[145-147]

The decrease of the barrier, 313 to 236 = 77 kJ·mol^{-1}, could be related to a difference in the geometry between a neutral 3-pyrazoline and a 2-pyrazolinium cation; the different pathways are apparent in Figure 12. However, a more important factor is that the difference in stability, which was –31.0 kJ·mol^{-1} for the neutral species (**156** more stable than **157**), changes sign to +52.8 kJ·mol^{-1} (**157H**$^+$ more stable than **156H**$^+$). One can tentatively conclude that with an acid catalyst the pathway would be **156** → **156H**$^+$ → **157H**$^+$ → **157**.

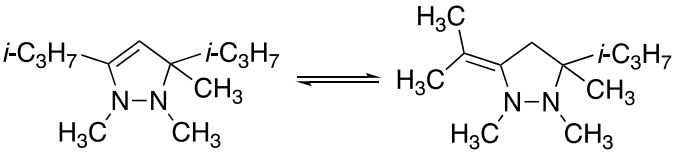
The *exo*/*endo* tautomerism of pyrazolines implies that the substituent at position 3 must be an XH group, OH, SH, NHR, CHRR', that is, groups such as H, C_6H_5, CRR'R'', COR, CO_2R, etc., cannot have *exo* tautomers. It is well known, for general tautomerism, that for CH_2R and CHRR' substituents to be stable as *exo* tautomers, the R groups should be COR, CO_2R or CN.[148] For this reason compounds **94**, **96** and **97** (Scheme 26) exist as *exo*-methylene-pyrazolidines.[103,104]



156a → 157a **156aH⁺ → 157aH⁺**

Figure 12. Transition states of 1,3-proton shifts.

The most important result was the determination of the tautomeric equilibrium constant K_T (*endo*/*exo* = 0.37, 0.32 and 1.0) and the dependence of K_T on the nature of the solvent for compound **171** (Scheme 44).[23]



171a **171b**

$CHCl_3$	27%	73%
Chlorobenzene	27%	73%
Nitrobenzene	24%	76%
Pyridine	50%	50%

Scheme 44. Presence of both *endo*/*exo* tautomers.

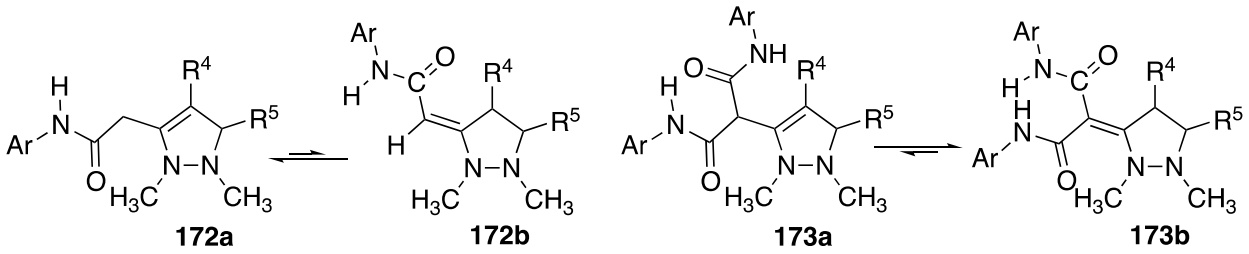
The equilibria between **171a** and **171b** were calculated at the [B3LYP/6-311++G(d,p)] level (Table 4).

Table 4. The *endo*/*exo* tautomerism of **171**

	% *endo* population			E_{rel} (kJ·mol^{-1})		
Endo	gas	nitrobenzene	pyridine	gas	nitrobenzene	pyridine
Experimental	---	24	50	---	2.7	0.0
Calculated	37.1	50.0	48.9	1.3	0.0	0.1

The calculation does not reproduce the solvent effects but the energy differences are very small, *i.e.*, less than 3 kJ·mol^{-1}.

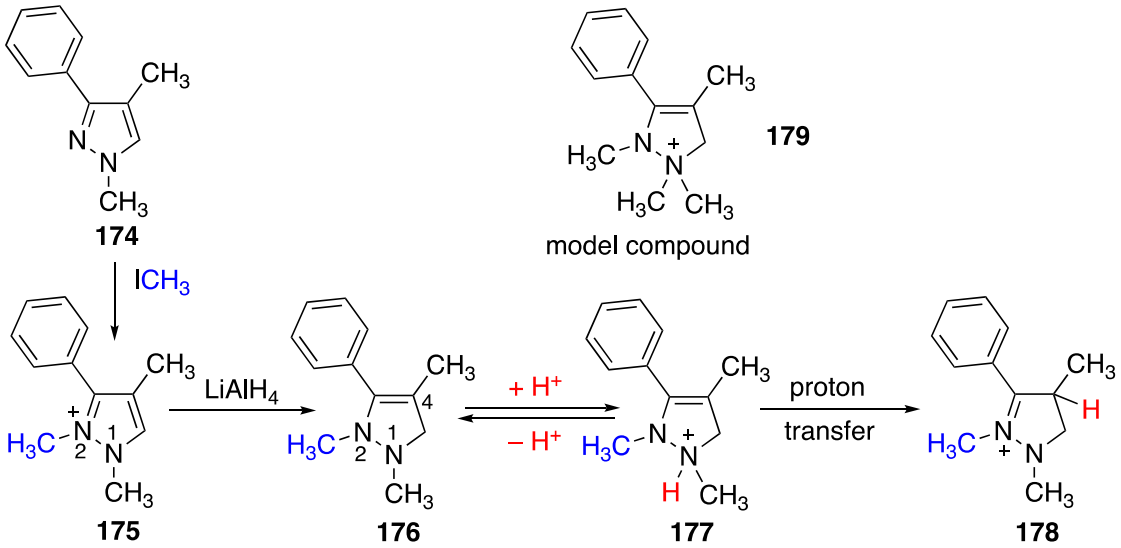
The Petrus group published a paper that contained some examples of *endo*/*exo* tautomerism (Scheme 45) where only one tautomer, **172a** and **173b**, was observed.[149]



Scheme 45. The effect of amide substituents on *endo*/*exo* tautomerism.

3.3. Basicity, protonation and quaternization

In a way similar to enamines,[150,151] 3-pyrazolines have a kinetic (on N1) and a thermodynamic (on C4) site of protonation, as partly illustrated in Scheme 43. We will now explain how that conclusion was reached; UV and ^{1}H NMR spectroscopies and quaternary ammonium salts (Section 3.4) were used as techniques and models.[92,152] The NMR approach will be illustrated using the oldest example, *i.e.*, 1,2,4-trimethyl-3-phenyl-3-pyrazoline (**176**) obtained by reduction of the pyrazolium cation **175** (Section 2.3.2) and using the quaternary salt **179** as a model (Scheme 46).[153] The identification of both methyl groups was carried out using deuteromethyl iodide instead of methyl iodide to quaternize pyrazole **174** – this labels the methyl group at position 2 of **175** resulting in the disappearance of the signals at 2.93 and 3.83 ppm (Figure 13).[133,153] The rate of the 1,4-proton transfer was determined and it has a first-order kinetic with a rate of $4*10^{-3}$ s^1.[153]



Scheme 46. 1,4-Proton transfer in 3-pyrazolines.

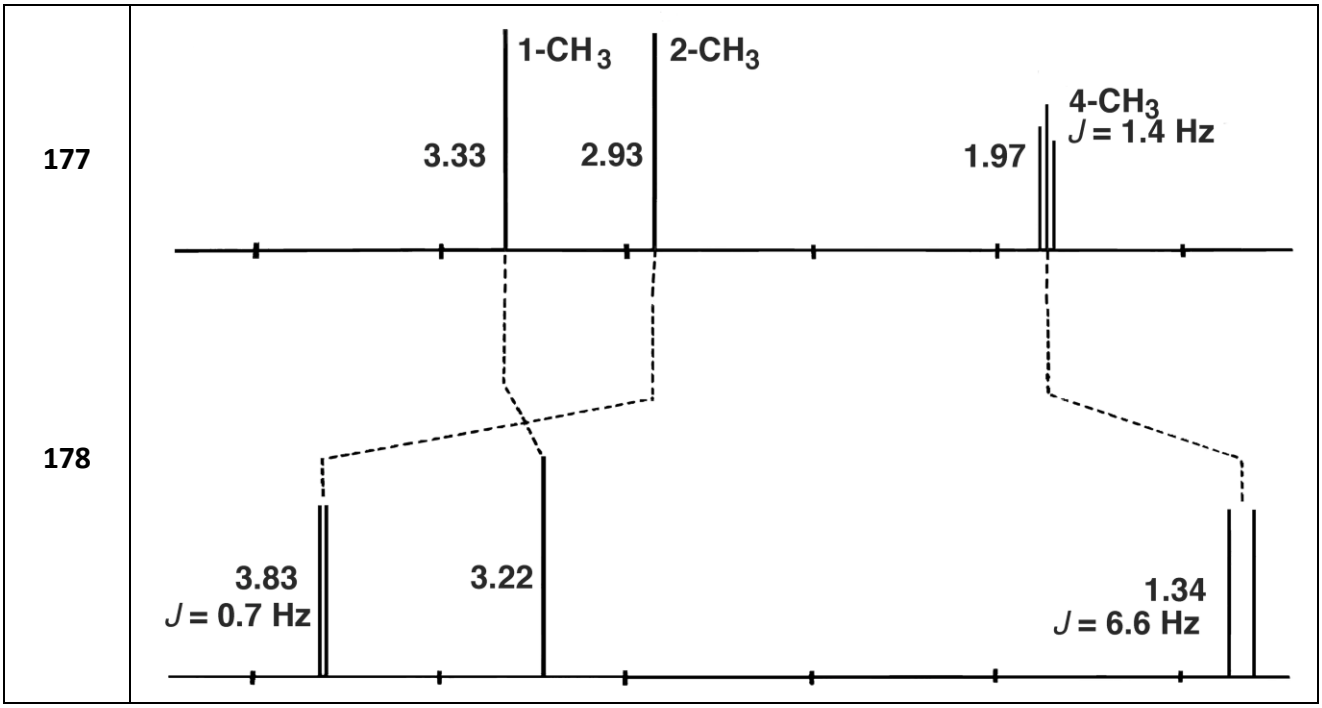
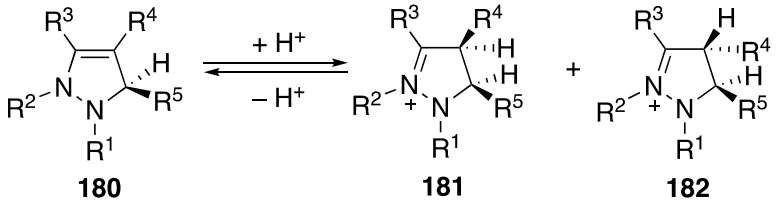


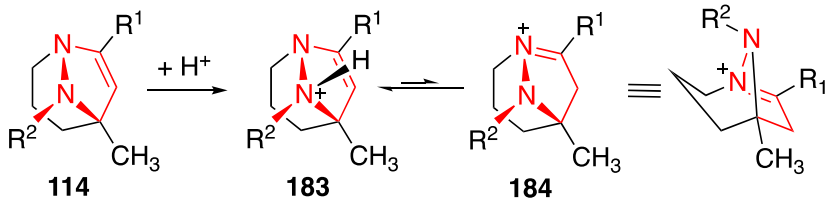
Figure 13. ^{1}H NMR spectra of compounds **177** and **178**.

In two subsequent papers the model in Scheme 46 was refined. In the first paper it was proposed that the origin of **178**, in addition to the isomerization of **177**, could be the result of a direct protonation of **176** or a second protonation of **177** on C4 followed by loss of the proton on N1.[154] In the second paper the stereochemistry of the C-protonation was discussed (Scheme 47). ^{1}H NMR experiments led to the conclusion that the protonation of 3-pyrazolines **180** affords the *trans* structure, *i.e.*, the thermodynamic one **182**; the kinetic one **181**, corresponding to an attack at the less hindered face, was not observed (Scheme 47).[155]



Scheme 47. Stereochemistry of the C-protonation of 3-pyrazolines.

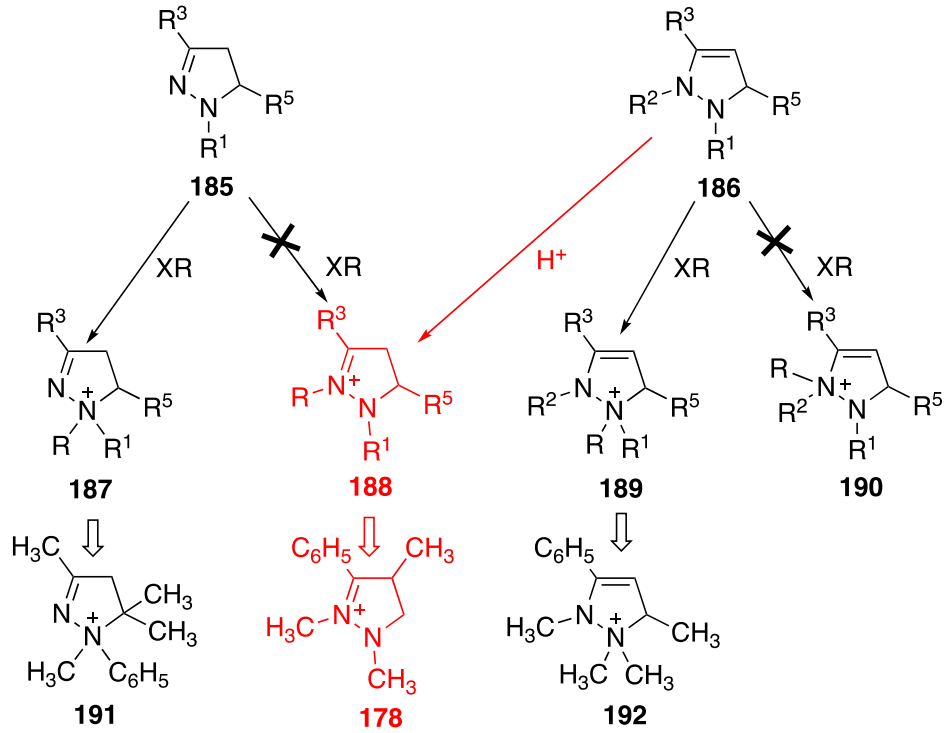
The kinetic (on N1) and thermodynamic (on C4) protonation of 3-pyrazolines can be hampered by the Bredt rule.[156,157] In the case of 3-pyrazolines **114** (Scheme 48)[117] the *C*-protonation would lead to the unstable cation **184** (Scheme 48), which is similar to bicyclo[3.2.1]oct-5-ene, and for this reason the *N*-protonated cation **183** would be stable.



Scheme 48. Possible result of the protonation of 3-pyrazoline **114**.

3.4. Reactions on the nitrogen atoms

In previous sections we have discussed quaternary structures (**13**, **19**, **23**, **156Hb**$^+$, **157Hb**$^+$, **178**, **179**, **181**, **182**). All of the possibilities starting from 2-pyrazolines **185** and from 3-pyrazolines **186** are shown in Scheme 49. Quaternization of 2-pyrazolines only produces **187** but **188** can be obtained by protonation of 3-pyrazolines **186**.



Scheme 49. Quaternization of 2-and 3-pyrazolines.

The only unknown quaternary salt is **190**; Hinman methylated compound **12** but the position of the new methyl group was not determined,[15] although the product most certainly has the structure **189**. Several examples of compounds **187**–**189** with different substituents are shown in Scheme 49; compound **178** has already been discussed (Scheme 46) and compounds **191**[158] and **192**[153] were described in old publications. Evidence that the methylation of **185** occurs at position 1, structure **187**, was provided by a ^{1}H NMR study of **191** as only this structure explains why the methyl groups at position 5 give two different signals, with one being *cis* to the methyl and the other *cis* to the phenyl group.[158]

3.5. Reactions of the C-substituents

There is only one publication in which the reactivity of a C-substituent of a 3-pyrazoline is discussed. The $Si(CH_3)_2Ph$ and $Si(C_6H_5)_2tBu$ groups of compounds **153**–**157** (Scheme 37) react with BF_3, I_2 and CH_3COCl to afford different 3-pyrazolines **193**, **194** and **195**, with elimination of the corresponding silanes (Figure 14). Compound **194** was not isolated since it is oxidized by iodine to a pyrazolium salt.[136]

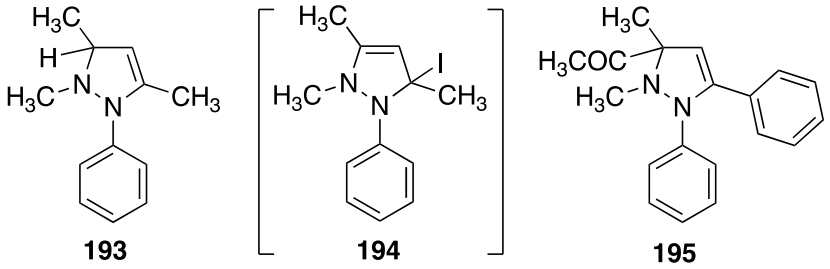
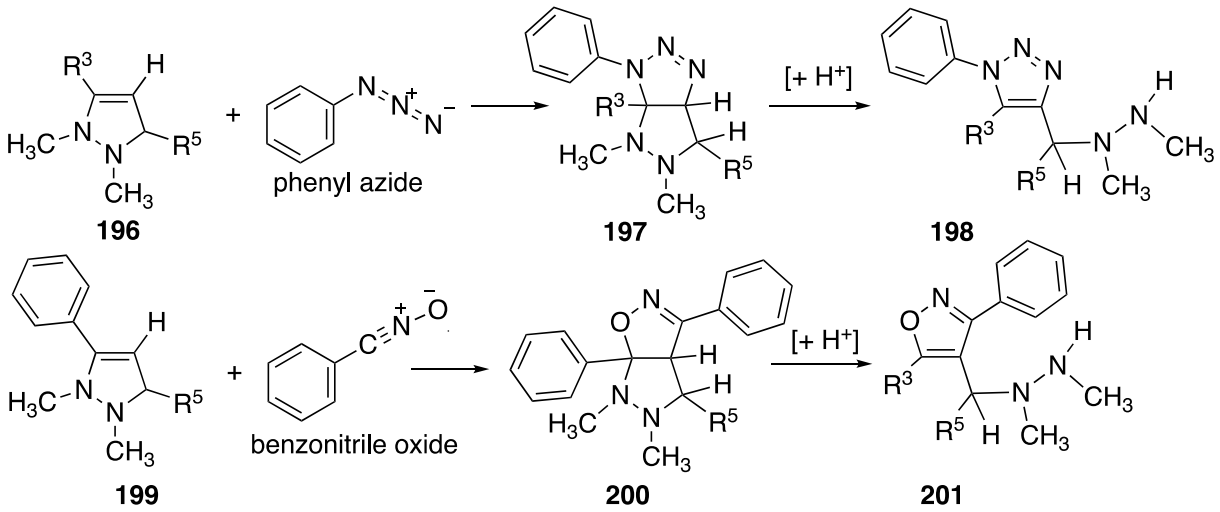


Figure 14. Pyrazolines prepared by elimination of silanes.

3.6. Reactions on the CC double bond

Petrus *et al*. published four important papers on a series of reactions of 3-pyrazolines with 1,3-dipoles that, depending on the dipole, lead to cycloadducts (Scheme 50) or to substitution reactions (enamine behavior, Scheme 51). Although several aryl groups were explored, only the phenyl groups are represented in Scheme 50.

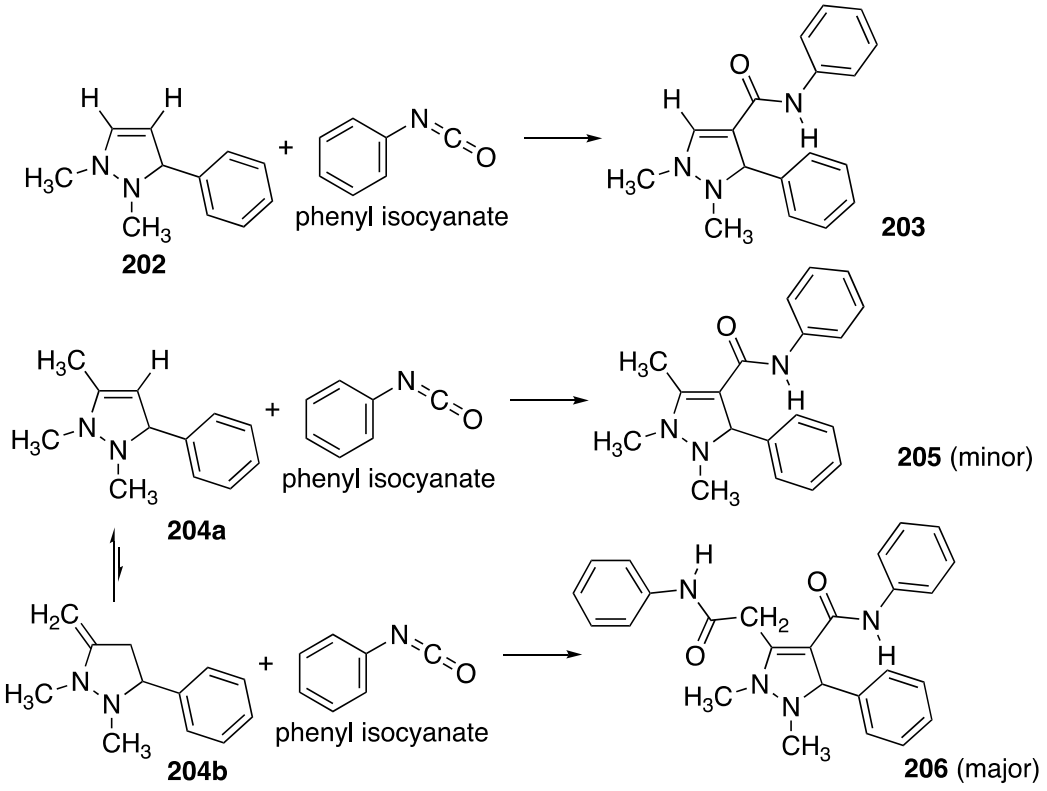


Scheme 50. Reactivity of 3-pyrazolines as dipolarophiles.

The reaction of **196** with phenyl azide led to a pyrazolidino-1,2,3-triazoline **197**, which opened in an acidic medium to give 1,2,3-triazole **198**.[150] Similarly, but on using benzonitrile oxide, **199** was transformed to **200**, which ring-opened to **201** in an acidic medium.[159]

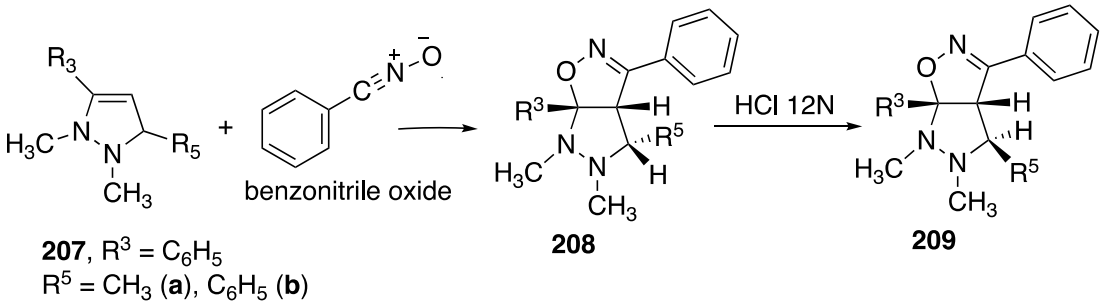
Different behavior was observed in the reaction with phenyl isocyanate, where **203** was obtained from **202** (Scheme 51).[160] The related case of compound **204** is more interesting; this compound exists in two tautomeric forms in rapid equilibrium, namely the *endo* **204a** and the *exo* **204b**, with the *endo* form being

predominant; however, in the reaction with phenyl isocyanate **205** is the minor isomer and **206** the major one.[161] The fact that the minor tautomer is the most reactive is known as the Gustafson paradox.[149,161]



Scheme 51. Reactivity of 3-pyrazolines as enamines.

The last paper of this group studied (Scheme 52) the stereochemistry of [3+2] cycloaddition of benzonitrile oxide on a 3-pyrazoline **207**, related to **199**, to give pyrazolidino[4,3-*d*]2-isoxazoline **208** (Scheme 52).[162] Two R^3R^5 *cis* products (Scheme 52) stereoisomers result on using a 3-pyrazoline disubstituted at positions 3 and 5, namely the R^3R^5 *trans* and the R^3R^5 *cis*. Epimerization of carbon C5 by treatment with 12N HCl partly transforms **208** into **209** by a mechanism that involves ring opening of the pyrazolidine.



Scheme 52. Cycloaddition of **207** with benzonitrile oxide and epimerization of **208** into **209**.

We calculated the energies of **208** and **209** in both the **a** and **b** series (Table 5).

Table 5. Relative energies (kJ·mol^{-1}) of the isomers **208** and **209** (Scheme 58).

	208a	**209a**	**208b**	**209b**
E_{rel}	0.6	0.0	0.0	5.3

In series **a** the result of the calculation is consistent with the epimerization of **208a** to **209a** but the value of E_{rel} is very weak. In series **b** the calculation yields the opposite effect. We also calculated the two approaches of benzonitrile oxide to pyrazoline **207a**; in this case the approach that yields **208a** is favored, with a barrier of 50.1 kJ·mol^{-1} compared to 86.2 kJ·mol^{-1}, which is consistent with the enamine behavior proposed by Jacquier *et al*.[150]

3.7. Oxidation

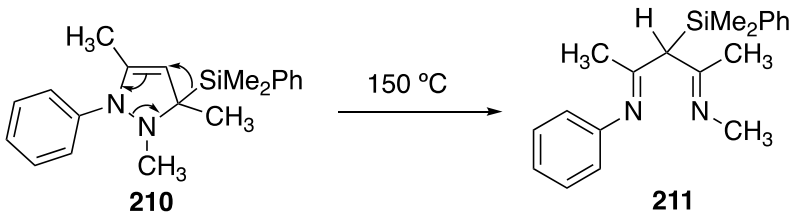
The formation of pyrazoles **109** and **110** from 3-pyrazolines **107** and **108**, which were not isolated, was shown in (Section 2.2.4).[113] 1,2-Dimethyl-3-phenyl-3-pyrazoline (**150**, $R^1 = R^2 = Me$, $R^3 = Ph$, $R^4 = R^5 = H$) was oxidized to 1,2-dimethyl-3-phenyl-3-pyrazolium chloride **149** by trityl chloride (Section 2.3.2); other 1,2-dimethyl-3,4-polymethylene-3-pyrazolines (Section 2.1.1) react with oxidizing agents to give the corresponding pyrazolium ions.[16]

3.8. Reduction

Several reducing agents have been used to reduce 3-pyrazolines to pyrazolidines: H_2/Pd-C,[15,126] $NaBH_4$,[130] B_2H_6,[155] and I_2 + $LiAlH_4$.[121] In latter case the mechanism was studied by using all combinations of $LiAlH_4$ and $LiAlD_4$ followed by treatment with H_2O and D_2O.

3.9. Rearrangement

The ring opening of **127** to afford **126** (Section 2.2.5) by irradiation was the first example of a rearrangement in these compounds.[120] Compound **127** undergoes a conrotatory 1,5-electrocyclic ring-opening reaction to give **126** photochemically. Although 5-silyl-3-pyrazolines are stable at room temperature, when compound **210** is heated at 150 °C, the ring opens by cleavage of the N–N bond with silicon rearrangement to give an α-silyl-β-diimine **211** (Scheme 53).[136]



210 **211**

Scheme 53. Rearrangement of 5-silyl-3-pyrazolines.

Huisgen *et al*. commented that examples of the rearrangement of 3-pyrazolines into 4-imidazolines were, and still are, lacking.[116]

4. Structure, Spectra, and Physical Properties

In this section we will highlight publications that contain specific discussions of the structure, spectra and physical properties of 3-pyrazolines. Publications that contain spectroscopic data in the experimental part only will not discussed. Note that older papers cite UV and IR results and, progressively, ^{1}H NMR data at low field, while more recent papers cite ^{1}H NMR and ^{13}C NMR data at high field and mass spectrometry data.

4.1. UV spectra

After two previous studies on the absorption of 3-pyrazolines,[132,163] a complete discussion was published in the years 1969–1970,[155] when a large number of 3-pyrazolines **212** were studied (Figure 15). The alkyl groups do not have any effect (λ_{max} = 235–245 nm, ε ~ 3000), the effect of the phenyl groups on the C atoms depend on the position, *i.e.*, 3-phenyl, cross-conjugation (λ_{max} = 270 nm, ε ~ 3000-6000), 4-phenyl, normal conjugation (λ_{max} = 300 nm, ε ~ 8000). The case of *N*-phenyl derivatives is more complex due to the presence of two maxima. Note that **212m** is **207a**.

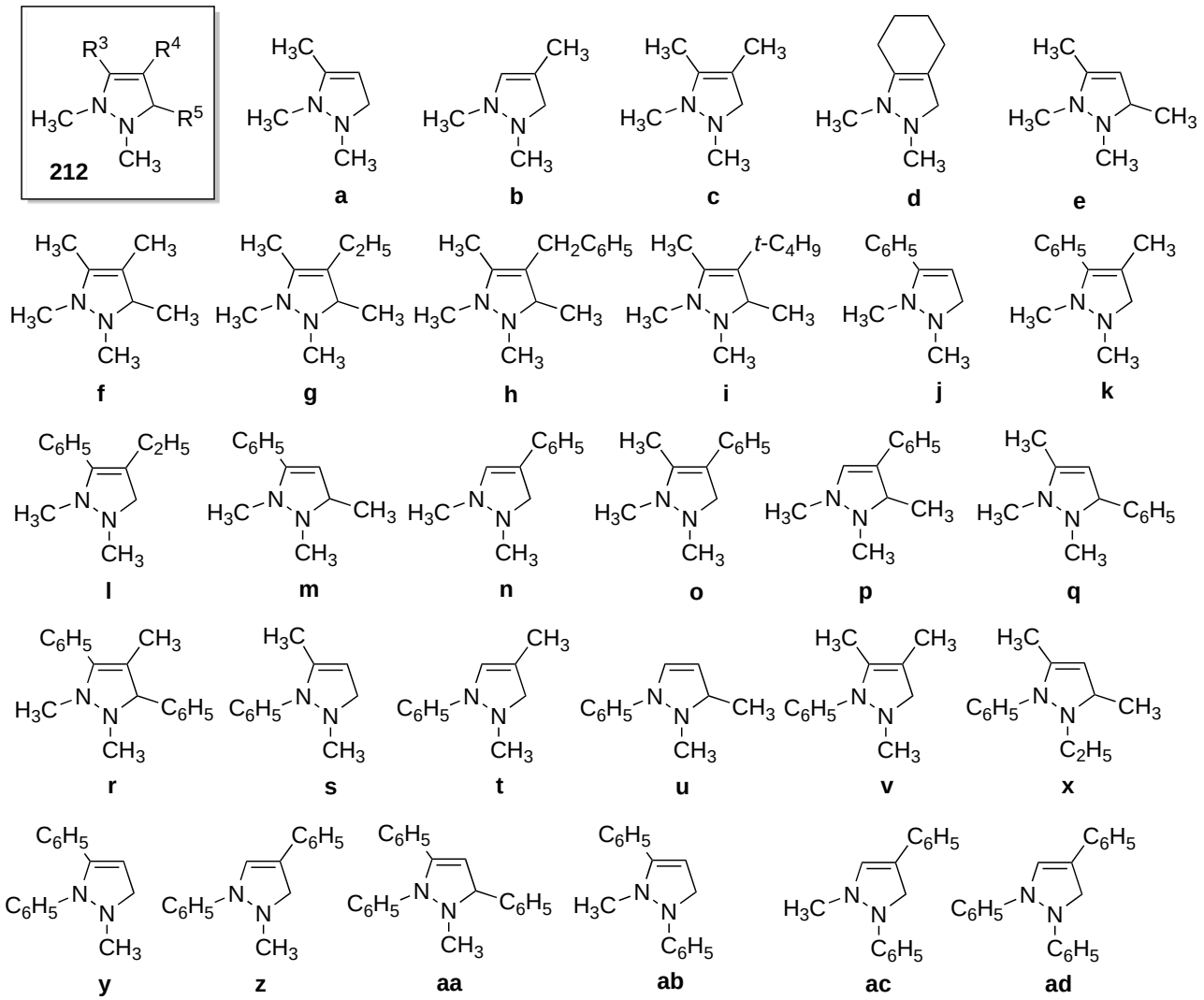


Figure 15. 3-Pyrazolines studied by UV/visible spectroscopy in 95% EtOH.

Electronic spectra are no longer routinely used to characterize a compound and the main points of interest are the photophysics and photochemistry of these compounds as well the theoretical calculations of these properties.

4.2. IR spectra

Hinman *et al*. indicated that 1,2-dimethyl-3-phenyl-3-pyrazoline **212j** (Figure 15) exhibits two characteristic bands in the IR spectrum (pure liquid): one at 1642 cm^{-1} attributed to the C=C double bond and the other at 1580 cm^{-1} attributed to the phenyl conjugated to the double bond.[15] Wagner-Jauregg and Zirngibl, with reference to the previous authors, assigned the reduction product of a pyrazolone as having a 3-pyrazoline structure because it exhibited a band at 1600 cm^{-1}.[125] We have shown that it is in fact a 2-pyrazoline, with the band at 1600 cm^{-1} being assignable to the phenyl at position 1.[126]

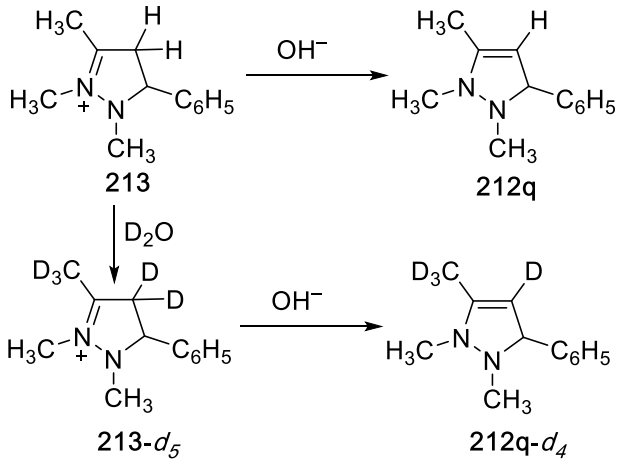
The 1,2-dimethyl-3-pyrazolines that we prepared (Figure 15) were studied by IR spectroscopy (solvent $CHCl_3$). The first UV group of Figure 15 (only alkyl substituents) showed a band at 1665–1675 cm^{-1} attributable to the C=C double bond (in enamines it is found at 1650–1660 cm^{-1}),[164] whereas the second UV group (*N*-phenyl substituents) showed two styryl bands (whether the phenyl is in position 3 or 4) at 1595–1600 and 1640–1650 cm^{-1}.

4.3. ^{1}H NMR spectra

At a time when NMR spectroscopy was limited to ^{1}H spectra recorded on low-field instruments, problems were solved 'chemically' with deuterium-labeled compounds and by analogy with model compounds. This was the era before Fourier Transformation, ^{13}C and ^{15}N NMR spectroscopies, and 2D experiments and it covers most of the publications from 1965 to 1973, during which 56.4 MHz, then 60 MHz and finally 100 MHz spectrometers were employed.

Our 1965 paper concerned the use of ^{1}H NMR spectroscopy to determine the structure of 3-pyrazolines **212j** and **212o**, including the *exo*/*endo* tautomerism in the latter case.[164]

We later reported a ^{1}H NMR study of 3-pyrazolines **212j**, **212k**, **212l**, **212m**, **212o**, **212p** and **212q**. The use of H/D exchange in 2-pyrazolinium salt **213** to afford **213**-d_5 enabled the preparation of the deuterated analog of **212q**, **212q**-d_4, which proved useful to identify some long-range ^{1}H-^{1}H spin-spin coupling constants (SSCC) (Scheme 54).[132,153]



Scheme 54. Deuteration at positions 3 and 4 of pyrazoline **212q**.

A similar study on pyrazolines **212a**, **212b**, **212c**, **212d**, **212e**, **212j**, **212k**, **212l**, **212m**, **212q** and **212o** also involved H/D exchanges but the major emphasis was on ^{1}H-^{1}H SSCC, for instance in compounds **212a** and **212k** (Figure 16).[155]

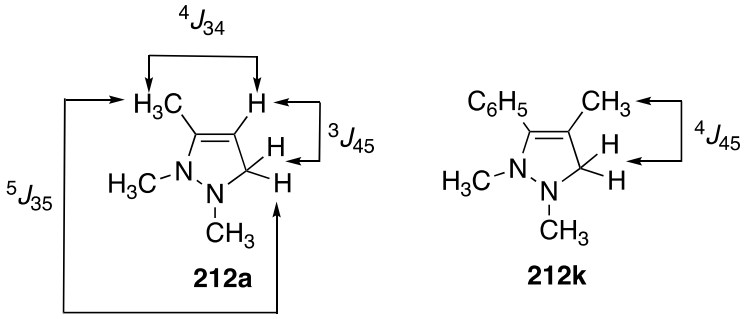


Figure 16. Long-range SSCC.

A classical example of diastereotopic protons was observed in the isopropyl groups of pyrazoline **214** (1.00 and 1.03 ppm) but not in **169** (1.02 ppm), possibly because the *i*-Pr group is further from the stereocenter at position 5 and because the ^{1}H NMR spectra were recorded at 60 MHz (Figure 17).[165]

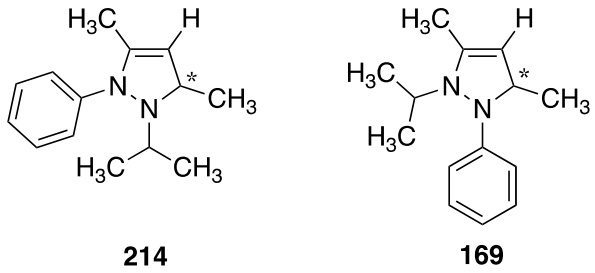
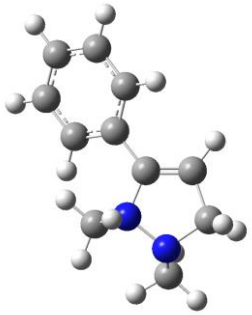
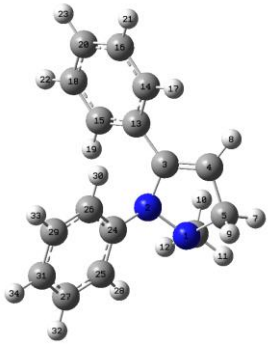


Figure 17. Chiral consequences of the methyl substituent at C5.

A major paper was published in 1970[154] on the NMR spectra of a large series of 3-pyrazolines recorded in $CDCl_3$. Amongst others, compounds **212f**, **212g**, **212h**, **212i**, **212j**, **212k**, **212m**, **212n**, **212o**, **212p**, **212r**, **212s**, **212t**, **212u**, **212v**, **212x**, **212y**, **212z**, **212aa**, **212ab**, **212ac** and **212ad** are represented in Figure 15. Besides the results reported in Figure 17, the CH_2 part of the 1-ethyl substituent of compound **212x** also presented diastereotopicity (2.84 and 2.00 ppm). Another aspect discussed in this paper is the successful application of the Matter, Pascual, Pretsch, Pross, Simon and Sternhell rules for olefins[166] to the C3C4 double bond of 3-pyrazolines.

Table 6. Torsion angles and ^{1}H chemical shifts of the phenyl groups of **212j** and **212y**.

Calculated minimum energy conformations		
3-Pyrazoline	**212j**	**212y**
Experimental $CDCl_3$	3-Ph: 7.30 (m)	3-Ph: 7.30 (m) *N*-Ph: 7.04 (m)
Calculated chemical shifts	3-Ph: 7.54 (*o*), 7.28 (*m*), 7.21 (*p*) Mean: 7.37	3-Ph: 7.55 (*o*), 7.28 (*m*), 7.23 (*p*) Mean: 7.38 *N*-Ph: 6.82 (*o*), 7.02 (*m*), 6.76 (*p*) Mean: 6.89
Torsion angles	3-Ph: 31.6°	3-Ph: 25.4°, *N*-Ph: 42.3°

Based on the ^{1}H chemical shifts in the NMR spectra at 60 MHz, the assignment of the C- and *N*-phenyl groups of 3-pyrazolines **212j** and **212y** was achieved (Table 6).[154] Calculations at the GIAO/B3LYP/6-311+G(d,p) level reproduced adequately these findings and provided information about the conformation of the phenyl groups.

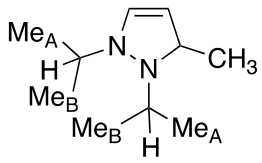
In 1973 ^{1}H NMR spectra were recorded at 100 MHz and experiments such as decoupling of *N*-methyl protons were carried out. [133] The increased precision allowed the creation of a model for the *N*-methyl groups that included the effects of the phenyl groups at positions 3, 4 and 5 on 1-methyl and 2-methyl chemical shifts.

In much more recent studies NMR was used to determine the inversion barrier of the N–R groups (Section 3.1, Table 3, compounds **169** and **170**) using 300, 400 and 500 MHz spectrometers to record the ^{1}H NMR spectra at different temperatures.[34,35] A paper dealing with theoretical calculations of 3-pyrazolines will be discussed in Section 4.7.[143]

4.4. ^{13}C NMR spectra

Kostyanovsky *et al*. reported the chemical shifts in $CDCl_3$ at 100.61 MHz of the methyl groups of the *N*-isopropyl substituents of compound **215** at 17.73 (Me_A) and 19.34 ppm (Me_B) for the 1-*i*Pr group and 19.60 (Me_A) and 19.77 ppm (Me_B) for the 2-*i*Pr group (Figure 18). For the 1-iPr group the anisochronism amounts to 160 Hz.[34] In the case of compound **170**, the methyl signals of the methyl groups at positions 1 and 2 are, as expected, different with shifts of 27.63 and 28.23 ppm.[35]

^{13}C NMR data for 3-pyrazolines have been reported in several recent papers, albeit without a detailed discussion[40,117] until an experimental and theoretical paper was published in 2021.[143]



215

Figure 18. The structure of pyrazoline **215**.

4.5. ^{15}N and ^{19}F NMR spectra

Experimental data have not been published for ^{15}N NMR spectroscopy of 3-pyrazolines and only calculated values are available.[143] For compound **43** (Scheme 10) the ^{19}F chemical and ^{19}F-^{19}F SSCC were reported.[42,43]

4.6. X-ray molecular structures

Exploration of the Cambridge Structural Database (CSD uses six capital letters called Refcodes)[167] yielded numerous 3-pyrazoline structures although some of them are not 3-pyrazolines but 2,3-dihydro-1*H*-indazoles **3**. We have already discussed some structures such as YAKYAK (Figure 1), UZIRUR (Figure 9) and ZEWBAH (Figure 10).

In Section 2.2.3 it was outlined how the difficult problem of assigning the bromo- and fluorophenyl groups of compound **99** was solved by X-ray crystallography (CEZDIV, Figure 19).[109]

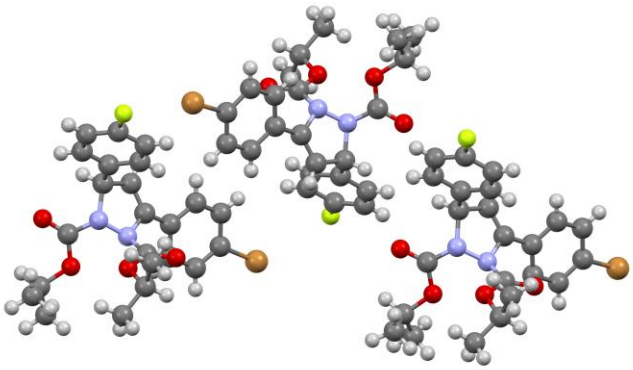


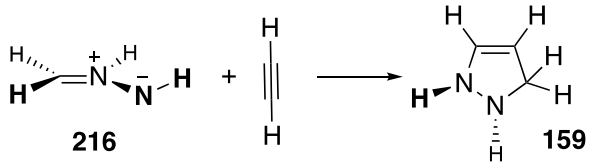
Figure 19. The three independent molecules of CEZDIV.

Many other structures of compounds cited previously have been determined, either as represented or with specific substituents instead of generic R groups: **26**, VEYBUW;[37] **48**, KULNOV;[47] **54**, AHEFEA,[64] and JADSOZ;[65] **57**, NECSEW;[66] **58**, YOHRIZ;[67] **61**, BEZTAD, BEZTASD01, OZEGUW;[69,70] **67**, UDAJIU;[79] **101**, UVUZUH;[110] **104** (PORLUG);[111] **113** (DAHKIG);[114] **121** (NUTRUQ);[119] **163** (AMZNON10);[140] and **165** (DAPZOJ).[141]

4.7. Computational results

As an essential component of structural studies, computational studies have been carried out on 3-pyrazolines by several authors, including ourselves. In one paper, the 3-pyrazoline fragment was included in a list of possible effects of pentagonal fragments on aromaticity.[168] Kraka, Cremer *et al*. studied theoretically the reaction of azomethine imine **216** with acetylene to afford the parent 3-pyrazoline **159** (Scheme 55); the level of the

calculations was CCSD(T)-F12/aug-cc-pVTZ.[169] The authors represented the 3-pyrazoline ring as being folded about N1···C4. [143]



Scheme 55. A theoretical study of a [3+2] cycloaddition.

Our contribution was reported in three papers.[143,144,170] The first paper[143] concerns the three pyrazoline isomers (Scheme 42) and the 3-pyrazoline structures, **159** and **168**, calculated [B3LYP/6-311++G(d,p)] are shown in Figure 20. For compounds **188** to **190** (Scheme 49), R = R^1 = R^2 = R^3 = R^5 = H.

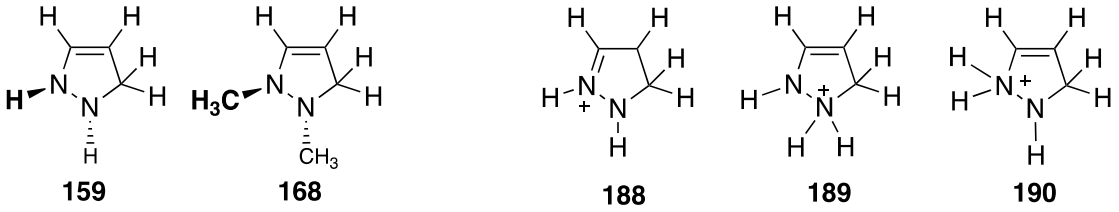
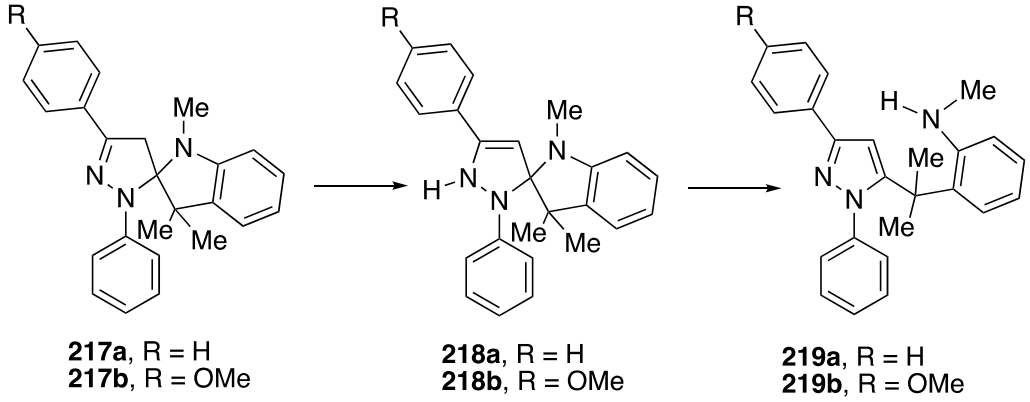


Figure 20. Theoretical calculations of simple 3-pyrazolines.

The study concerns conformational aspects (ring folding and N inversions of **159** and **168**, Section 3.1), tautomerism between 1-, 2- and 3-pyrazolines and between cations (Section 3.2), protonation (compounds **188**–**190** Section 3.4) and GIAO (Gauge-Independent Atomic Orbital) calculations of chemical shifts of all compounds in Figure 20.[144]

We devoted a paper[170] to the analysis of two publications by Hamme II *et al*. and these are summarized in Scheme 56. [171,172]



Scheme 56. Structures of the compounds studied by Hamme II.

In the first paper (series **a**, R = H) the authors explained that the formation of pyrazole **219a** (X-ray structure, refcode CORTEJ) from 2-pyrazoline **217a** involves a non-isolated 3-pyrazoline **218a**.[172] Our calculations

agree with the data reported for the isolated compounds **217a** and **219a**, including a hydrogen bond between the N–H and the π-system of the pyrazole ring.[171]

The second paper is more contentious and it concerns series **b** (R = OMe).[173] The X-ray structure of **217b** was represented but the depository number with CCDC (701051) corresponds to **219a** and the structure of **217b** was never deposited in the Cambridge Structural Database. The authors studied the dependence of the **217b**/**218b** equilibrium on the solvent ($CDCl_3$, C_6D_6, CF_3CO_2H) but we demonstrated that 3-pyrazoline **218b** was in fact pyrazole **219b**.[171]

One of our two last papers[143] concerns the structural and spectroscopic properties of the compounds gathered in Figure 21 calculated at the [B3LYP/6-311++G(d,p)] level; some of these compounds have already been discussed and others are new (**220** to **225**). The aspects covered include the conformation of the five-membered ring and the inversion of N–R substituents (Table 3, Section 3.1.) and the calculation of chemical shifts (^{1}H -Section 4.3- ^{13}C -Section 4.4- and ^{15}N -Section 4.5) using the GIAO approximation.

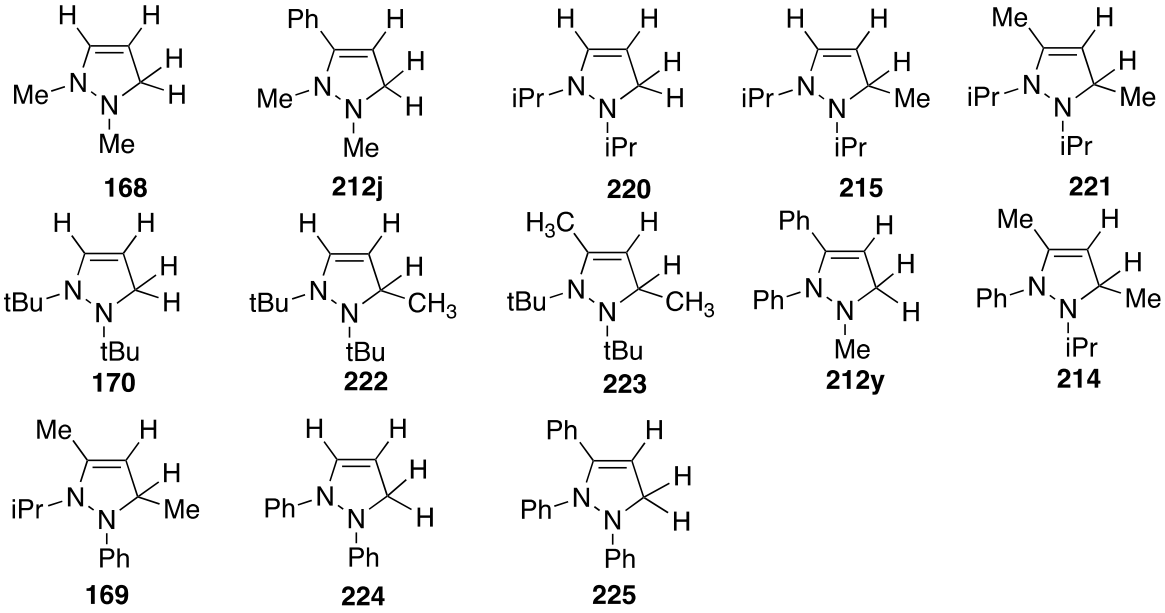


Figure 21. 3-Pyrazolines studied theoretically.

The calculated profiles of the *trans* epimerization and *cis*/*trans* isomerization of compound **168**, the simplest of the 1,2-disubstituted-3-pyrazolines, are provided in Figure 22. Both TSs, namely TS1 and TS2, which correspond to the inversion barriers of N2–Me (low barrier) and N1–Me (high barrier), respectively, were calculated. There are two *trans* enantiomers and therefore the double nitrogen inversion corresponds to enantiomerization processes (Figure 22). The fact that TS1 < TS2 is a consequence of the stabilization of TS1 by conjugation with the C3C4 double bond. The two *cis*-isomers are enantiomers.

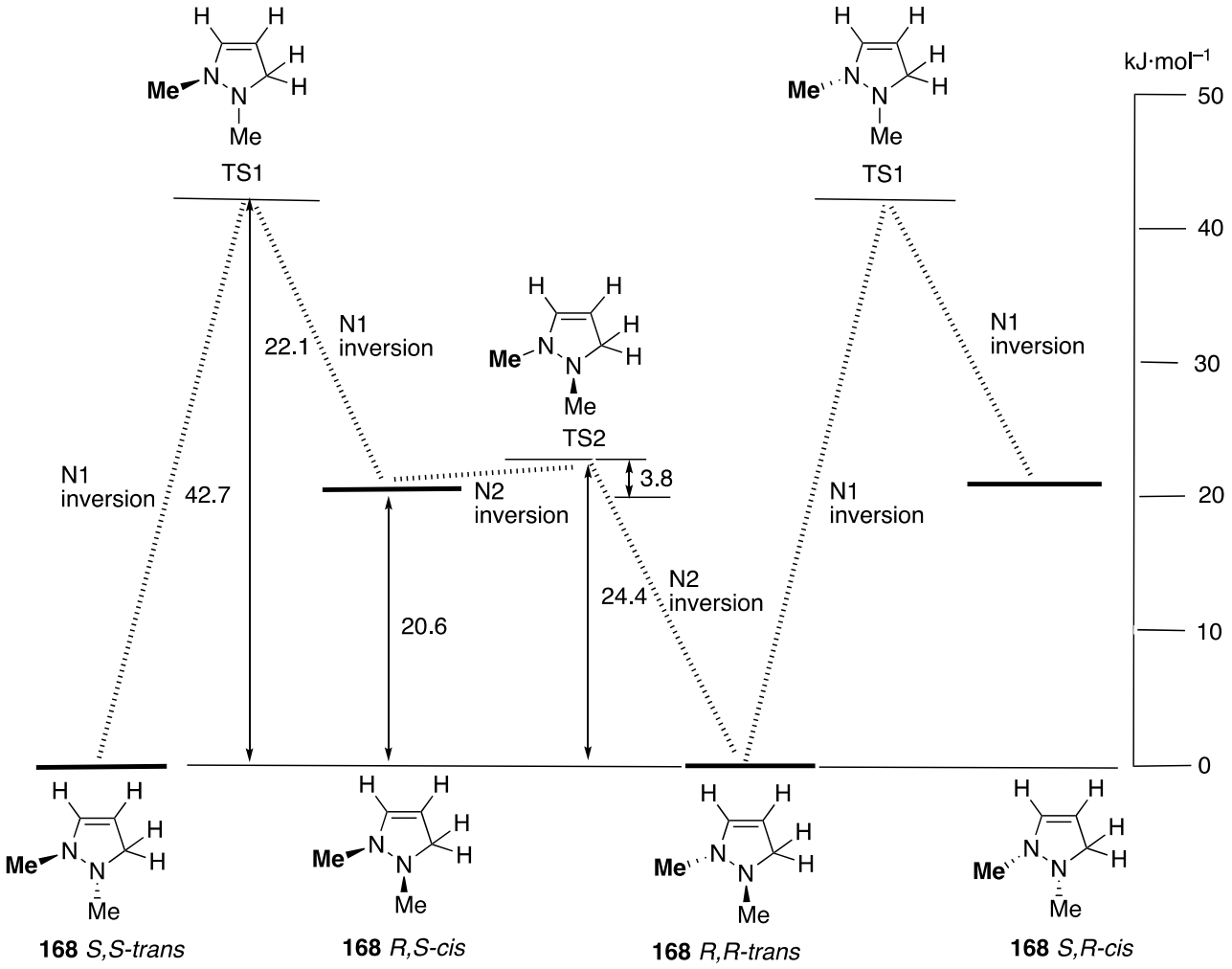


Figure 22. Profile of the inversion processes occurring in 1,2-dimethyl-3-pyrazoline.

The ^{1}H, ^{13}C and ^{15}N NMR chemical shifts were calculated for the most stable conformer (**168** *trans*) using [GIAO/B3LYP/6-311++G(d,p)]. Begtrup reported in 1973 that the conformation about the N1-C*ipso* bond of the *N*-phenyl group of azoles is related to the difference in chemical shifts between C*meta* and C*ortho* (C*m*–C*o*).[173] This method, which provides a qualitative assessment of the degree of interannular conjugation,[174] was based on ^{13}C chemical shifts determined in solution and semi-quantitative considerations about steric effects that must rotate the phenyl group.[175,176] This method was recently applied to phenyl pyrazoles using experimental chemical shifts and dihedral angles ϑ calculated by molecular mechanics.[177] Concerning the 3-pyrazolines of the reported paper,[143] two equations of medium quality were found:

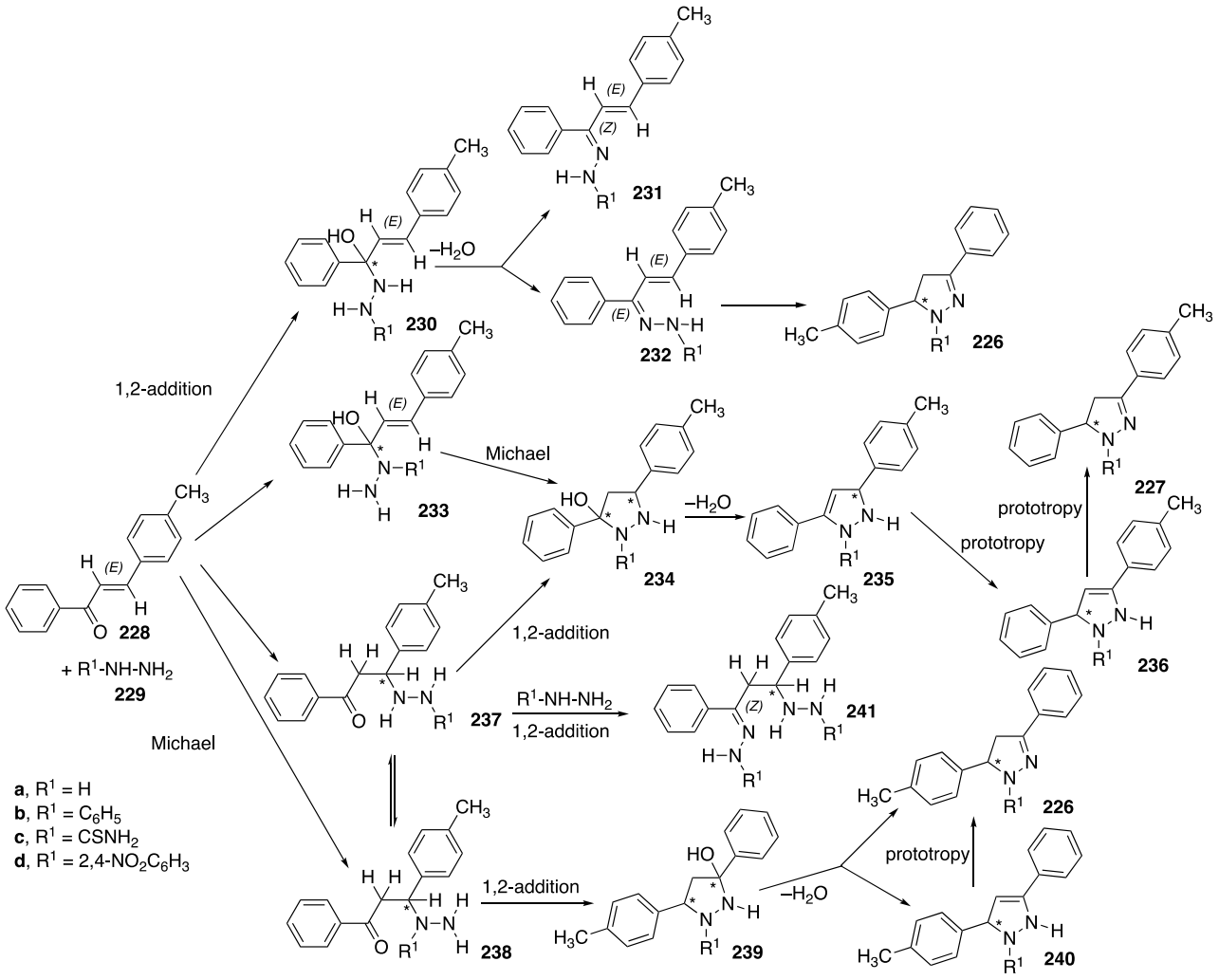
C*m*–C*o* = (13.8±1.4) – (0.21±0.02) ϑ, n = 17, R^2 = 0.83, RMS residual = 3.1 ppm

C*m*–C*o* = –(3.6±1.2) + (15.9±2.0) $\cos^2\vartheta$, n = 17, R^2 = 0.82, RMS residual = 3.2 ppm

Using the 80 available experimental ^{1}H and ^{13}C NMR data our calculations agree remarkably well:

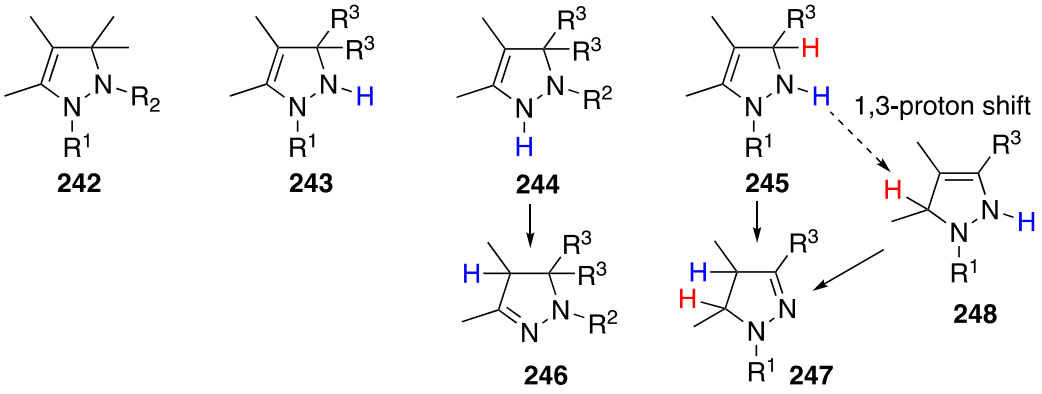
^{1}H & ^{13}C: Exp. = (1.016±0.004) Calc., R^2 = 0.999, RMS residual = 1.4 ppm,

The second of our last two papers concerned the mechanism of formation of 2-pyrazolines **226** and **227** starting from *p*-methyl-chalcone **228** and four hydrazines **229a**, **229b**, **229c** and **229d**.[145] The mechanism provided in Scheme 57 involves carbinolamines **230** and **233**, hydrazones **231** and **232**, hydroxypyrazolidines **234** and **239**, Michael addition compounds **237** and **238** and 3-pyrazolines **235**, **236** and **240** (**240a,b,c** were reported previously with the numbers **29**, **30** and **33**). A double addition product **241** was also characterized.



Scheme 57. Different mechanisms for the formation of 2-pyrazolines **226** and **227**.

One of the intriguing aspects of Scheme 57 concerns the transformation **235** → **227**. Compound **235** is a 3-pyrazoline that some authors called a 4-pyrazoline by numbering the ring from the *N*-substituted atom. The stability, in the sense of the reason why 3-pyrazolines do not isomerize into 2-pyrazolines, is summarized in Scheme 58.



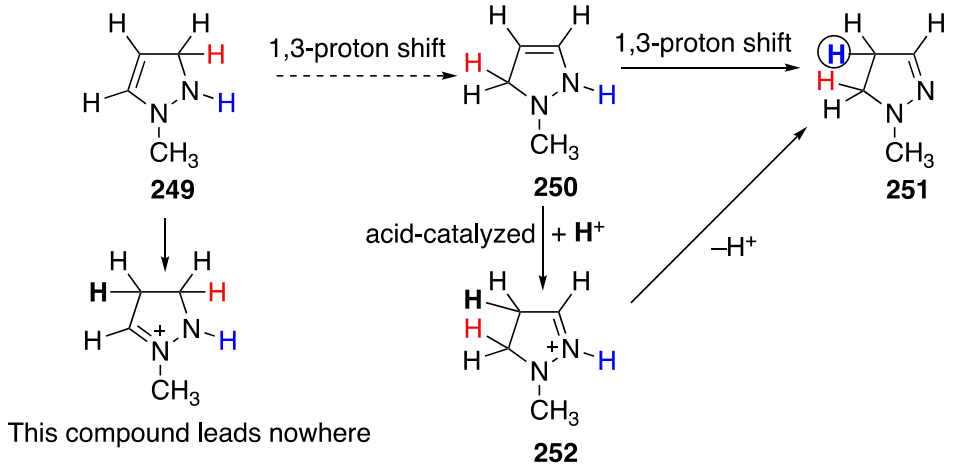
Scheme 58. The 3- to 2-pyrazoline isomerization channels.

1,2-Disubstituted 3-pyrazolines **242** and 3,3'-disubstituted 3-pyrazolines **243** cannot isomerize into 2-pyrazolines; 2,3,3-tribstituted-3-prazolines **244** isomerize to 2-pyrazolines **246**, the R^3 substituents can be H or different from H, the process corresponds to an enamine/imine[178-181] or enehydrazine/hydrazone[23,182-185] tautomerization. The most important result is the transformation **245** → **247**, which is equivalent to **235** → **227** (Scheme 59); **235** has never been isolated or detected in any of the studies cited previously. Both steps in the processes **245** → **248** → **247** (model compounds) and **235** → **236**→ **227** (Scheme 58) are 1,3-sigmatropic shifts that are forbidden by symmetry.[146-148] The difference is that the first step is a classical CH to C process while the second step is an NH to C process and this can modify the barriers to proton transfer. Both processes were calculated and the results are given in Table 7.

Table 7. Energetics (in kJ·mol^{-1}) of the tautomerization between 3- and 2-pyrazolines

Model	**249**	TS	**250**	TS	**251**
	60.8	355.1 [294.3]	63.1	330.4 [267.3]	0.0
Scheme 2	**235a**	TS	**236a**	TS	**227a**
	57.7	343.2 [285.5]	57.1	346.3 [289.2]	0.0

Both two-step profiles are very similar (actually, proportional, R^2 = 0.996). Both 3-pyrazolines, **249** and **250**, are very similar in energy because the only difference is the position of the *para*-methyl group; the 2-pyrazolines **251** are much more stable than the 3-pyrazolines. The first step, a 3-pyrazoline **249** to another 3-pyrazoline **250**, has a barrier of ~290 kJ·mol^{-1} and the second step, a 3- to 2-pyrazoline, has a slightly lower barrier of ~280 kJ·mol^{-1}. Therefore, both steps are forbidden and under neutral conditions the 3-pyrazolines should be stable.



Scheme 59. Isomerization of 3-pyrazolines into 2-pyrazolines (model).

In acid-catalysis conditions, since protonation of 3-pyrazolines affords 2-pyrazolinium cations,[153,156,164,186] the mechanism through **252** allows the transformation of **250** into **251** (Scheme 59). A series of calculations concerning Swarnkar 3-pyrazolines **29**, **30** and **33** (Scheme 9, R = CH_3)[39] are reported below (Figure 23 and Table 8).

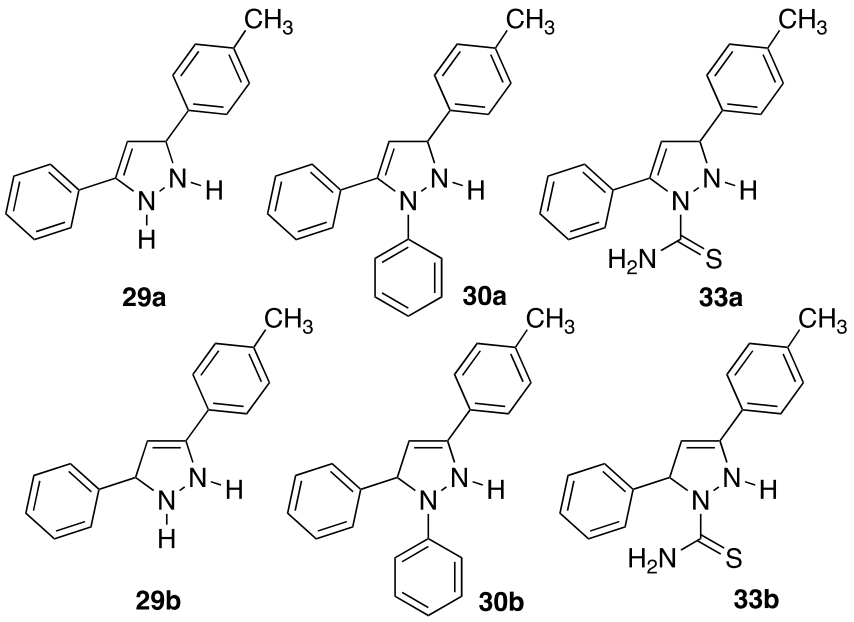


Figure 23. The two kinds of 3-pyrazolines.

Table 8. Energetics (in kJ·mol^{-1}) of the tautomerism between 3-pyrazolines

	a	b	c
10	0.6	14.6	35.8
11	0.0	0.0	0.0

The results in Table 8 indicate that – with the exception of the **29** series, where both isomers have the same energy due to the weak perturbation of the methyl group – in the **30** and **33** series tautomer **b** is clearly the most stable. However, this does not exclude structure **a** as a kinetic product in neutral media (see the preceding section)

5. Biological Properties

Very few 3-pyrazolines have been reported as having important biological activities, although they have been considered as fragments in protein binding sites. [187] In the field of anticancer agents (Figure 24) compounds **253** and **254** have received attention in recent years and the most active compound in the **254** series is **254a**.[188-190]

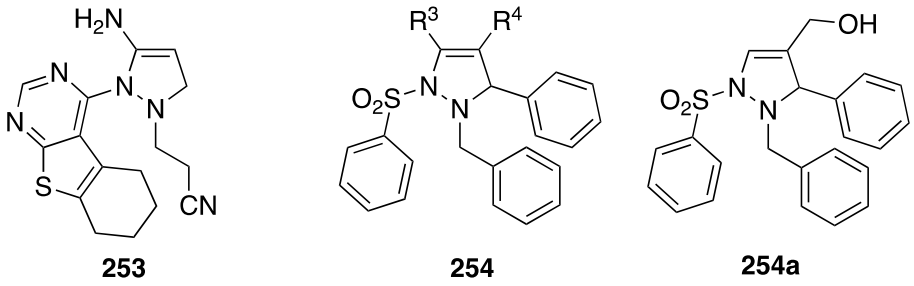


Figure 24. Anticancer 3-pyrazolines.

Older but much more widely studied compounds are Lilly's antibiotics (Figure 25). [83,191-193]The most studied compound is **LY 186826** and this was prepared by the procedure represented in Scheme 24; the main contributors were Stanovnik, Svete *et al*. [84,194-197]Some authors have used the same synthetic procedure and classify these compounds as pyrazolidinones (red part). [76]

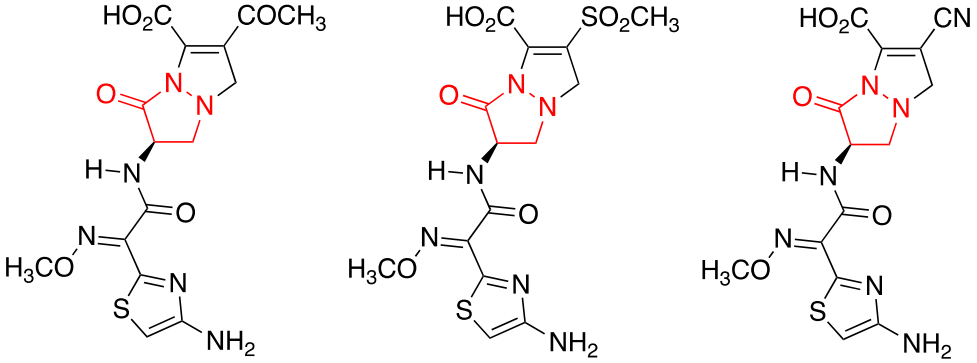


Figure 25. Lilly's antibiotics.

6. Conclusions

The main conclusions of the present review are:

1. The synthetic approaches to 3-pyrazolines cover many aspects of heterocyclic chemistry, including hydrazines, hydrazides, [3+2] dipolar cycloadditions, electrocyclic reactions and oxidation-reduction reactions.

2. Structural studies cover the double inversion at nitrogen atoms, tautomerism between different pyrazolines (position of the *endo* CC double bond) as well as the *endo*/*exo* tautomerism. The cations, pyrazolinium salts, resulting from the protonation of 3-pyrazolines also show prototropy.

3. The rich reactivity of 3-pyrazolines covers aspects such as the reactivity of the nitrogen atoms, the CC double bond as a dipolarophile, and rearrangements.

4. UV, IR and NMR results are abundant and have been reported in detail by several groups. Several X-ray structures were used to clarify some structural aspects.

5. Computational results from the literature and those obtained specifically for this review [GIAO/B3LYP/6-311++G(d,p)] proved useful to discuss certain aspects.

6. The scarce but interesting 3-pyrazolines with pharmacological properties are included in this review.

6. Acknowledgments

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