Synthesis of 2-Pyrazolines by the Reactions of α,β-Unsaturated Aldehydes, Ketones, and Esters with Diazoalkanes, Nitrile Imines, and Hydrazines

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Dedicated to Professor Dr. Waldemar Adam on the occasion of his 65th birthday.

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1. Introduction.

It was in the late nineteenth century that Fischer and Knövenagel described the reaction of acrolein with phenylhydrazine [1] to provide a pyrazoline type compound. Their experiment seems to be the first example of pyrazoline formation by the reaction of an α,β-enone with a hydrazine derivative. Later, Auwers *et al.* [2,3] corroborated that the product of this reaction was 1-phenyl-2-pyrazoline. During the last century, after these pioneering studies, numerous 2-pyrazolines were synthesized by the reaction of α,β-enones with hydrazines. This simple and convenient procedure has remained one of the most popular methods for the preparation of 2-pyrazolines.

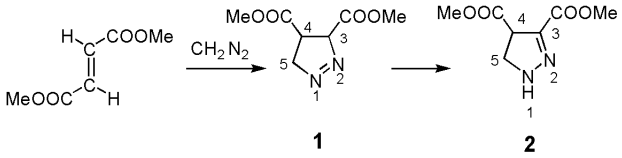
Concerning the synthesis of pyrazolines, the second milestone was the discovery of the reaction of the diazoalkanes with α,β-unsaturated carboxylic acid derivatives [4-7] and α,β-enones [8,9] in the early twentieth century. Among diazoalkanes, diazomethane proved to be the most convenient nitrogen-containing reagent making available the preparation of a wide variety of 1-pyrazolines as primary products which spontaneously isomerize or can be converted into their appropriate 2-pyrazoline isomers [10-14].

Various pyrazoline derivatives were found to possess important biological and pharmaceutical activities which stimulated research activity in the field of these nitrogen-containing heterocyclic compounds. Some examples of their most important effects include antimicrobial [15], central nervous system [16] and immunosuppressive [17] activities. Although 2-pyrazolines appear to be useful compounds in drug research, their syntheses have been reviewed in only a few accounts [18-20]. For this reason, the major aim of our present review article is to compile and discuss the most important procedures developed for the preparation of 2-pyrazolines. We concentrate mainly on those methods

which utilize the reaction of α,β-unsaturated aldehydes, ketones and esters with nitrogen-containing reagents like diazomethane, hydrazines and nitrile imines.

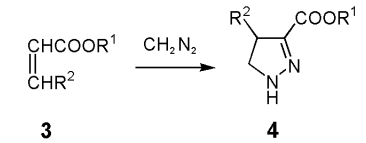
2. Synthesis of 2-Pyrazolines by the Reaction of α,β-Unsaturated Carboxylic Acid Esters with Diazoalkanes.

Diazomethane was first synthesized by Pechmann in 1894 from *N*-nitrosourethane by its reaction with potassium hydroxide [21]. The diazomethane gave a pyrazoline type compound on its reaction with dimethyl fumarate [21]. Later, it was corroborated [4] that the mechanism of this reaction was correctly anticipated by Pechmann. Namely, the primary product of this 1,3-dipolar cycloaddition is a 1-pyrazoline **1** which spontaneously isomerizes into its thermodynamically more stable 2-pyrazoline isomer **2** by a 1,3-H shift (Scheme 1).



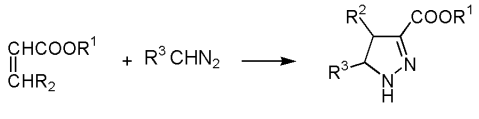
1 **2**

Reaction of α,β-unsaturated carboxylic acid esters and diazomethane has been thoroughly studied by Auwers *et al*. [4-7]. The preparation of a wide variety of 2-pyrazoline-3-carboxylic acid esters can be considered as a major result of their detailed synthetic studies. The reaction of acrylic acid and β-substituted acrylic acid esters **3** provided 4-substituted 2-pyrazoline-3-carboxylic acid esters **4** (Scheme 2) [4-7,21,22]. 5-Substituted and 4,5-disubstituted 2-pyrazoline-3-carboxylic acid esters **6** have been synthesized by the reaction of α,β-unsaturated carboxylic acid esters **3** with substituted diazomethanes **5** (Scheme 2) [4,10,23]. 5,5-Diphenyl-3-(methoxycarbonyl)-2-pyrazoline (**8**) has been synthesized by a base-catalyzed isomerization of 1-pyrazoline **7** obtained as a primary product of the cycloaddition of methyl acrylate with diphenyldiazomethane (Scheme 2) [24].



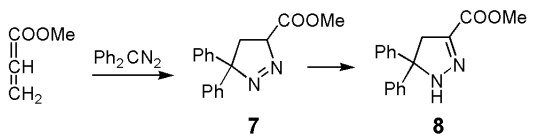
3 **4**

R^1: Me, Et; R^2: H, Me, Ph



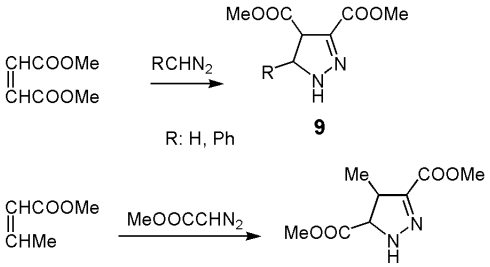
3 **5** **6**

R^1: Me, Et; R^2: H, Me, Ph; R^3: H, Me, Ph, COOEt



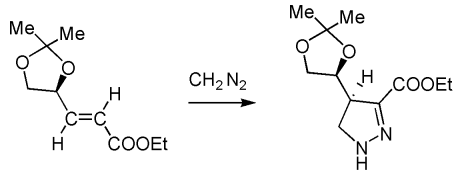
7 **8**

2-Pyrazoline dicarboxylic acid esters have been synthesized by the reaction of unsaturated dicarboxylic acid esters with diazoalkanes [4,5,10,13,23]. When dimethyl fumarate or maleate were allowed to react with diazoalkanes 3,4-dicarbomethoxy-2-pyrazolines **9** were obtained (Scheme 3) [10,21,23]. While the reaction of the methyl diazoacetate with methyl crotonate provided 3,5-dicarbomethoxy-4-methyl-2-pyrazoline (**10**) (Scheme 3) [23].



Thermal denitrogenation of the pyrazoline carboxylic acid derivatives affording cyclopropanes has also been thoroughly investigated by several research groups [10,13,23,24]. This reaction proved to be a simple and convenient procedure for the preparation of cyclopropane derivatives.

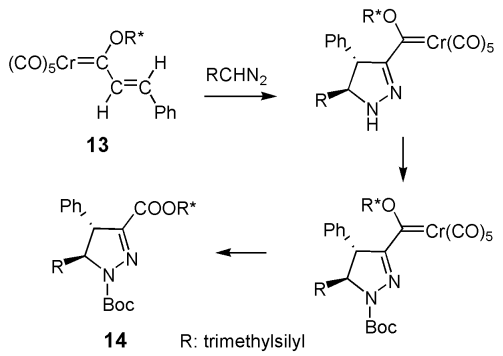
As far as the synthesis of 2-pyrazoline carboxylic acid derivatives is concerned, two recent developments, *viz.* the preparation of optically active derivatives, are noteworthy. Galley *et al*. synthesized optically active 2-pyrazoline derivative **12** by a stereoselective 1,3-dipolar cycloaddition of the optically active ester **11** with diazomethane (Scheme 4) [25]. However, this synthetic method itself is not new since the starting material can be considered to be a β-substituted acrylic acid ester, the cycloaddition of which with diazoalkanes is a well established procedure for the synthesis of pyrazolines.



11 **12**

The optically active 2-pyrazoline derivative **14** has been synthesized from the reaction of chromium carbene complex **13** derived from (-)-8-phenylmenthol and diazomethane followed by several reaction steps (Scheme 5)

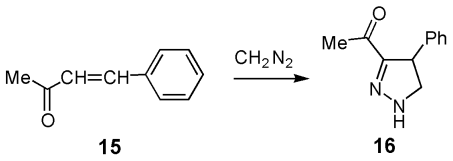
[26]. This procedure utilizes an optically active alcohol as a chiral auxiliary for the diastereofacial differentiation.



3. 1,3-Dipolar Cycloaddition of α,β-Enones and Diazoalkanes.

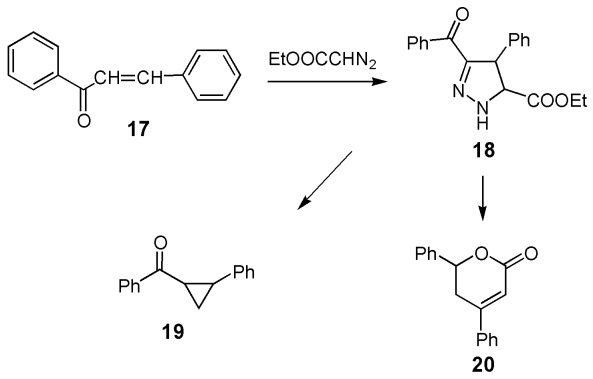
3.1. Reaction of Chalcones and Related α,β-Unsaturated Ketones with Diazomethane.

Preparation of 3-acetyl-4-phenyl-2-pyrazoline (**16**) by the reaction of benzylideneacetone (**15**) with diazomethane (Scheme 6) is probably the first example of the synthesis of a pyrazoline from the reaction of an α,β-unsaturated ketone and diazomethane and was published by Azzarello in 1906 [27]. Later, this reaction was reinvestigated by Smith and Howard [28] and by Raju and Rao [29] and the assumption made by Azzarello were corroborated.

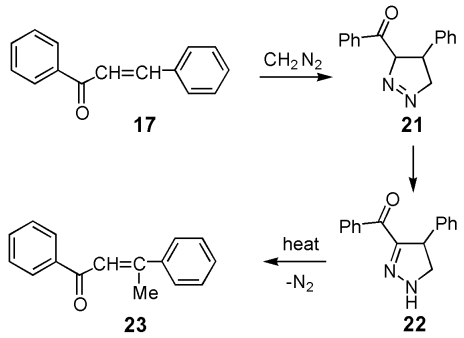


Also in the early twentieth century the reaction of chalcone (**17**) and the ethyl diazoacetate was performed by Kohler and Steele in 1919 [8]. The obtained pyrazoline **18** was supposed to yield a cyclopropane derivative **19** and pyrone **20** on thermal denitrogenation (Scheme 7). However, owing to the lack of an unambiguous instrumental structure elucidation of the pyrazoline synthesized, nowadays it is impossible to judge whether the 1-pyrazoline or 2-pyrazoline isomer was actually isolated in this experiment.

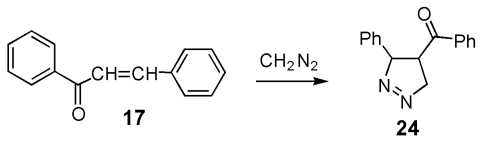
1,3-Dipolar cycloaddition of chalcone (**17**) and diazomethane was first investigated by Smith and Pings [9] and 3-benzoyl-4-phenyl-1-pyrazoline (**21**) was prepared as a primary product which was then isomerized into the 3-benzoyl-4-phenyl-2-pyrazoline (**22**) on gentle heating. Substance **22** yielded β-methylchalcone (**23**) on thermal denitrogenation



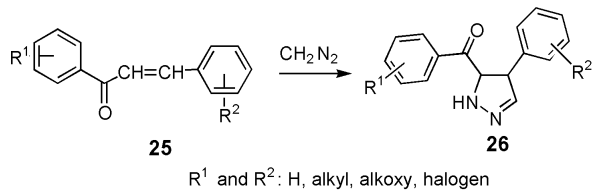
which proves that the cycloadditon of the chalcone and the diazomethane is regioselective (Scheme 8).



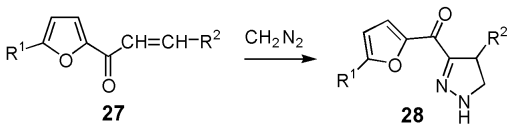
Later, Gathe *et al.* [30] described this reaction of the chalcone (**17**) to provide the isomeric 4-benzoyl-3-phenyl-1-pyrazoline (**24**) (Scheme 9), but on the basis of the published melting point value, their product was presumably 3-benzoyl-4-phenyl-2-pyrazoline (**22**) (*cf.* Scheme 8). Since no spectral data were published in their paper [30], only the melting point value can be used for comparison.



Reaction of variously substituted chalcones **25** and diazomethane has been studied by Mustafa and Fleifel [31] as well as by Sayed and Kjosen [32], but probably because of a misinterpretation of the ^{1}H nmr spectra, formation of 5-benzoyl-4-phenyl-2-pyrazoline (**26**) was misdescribed by both research groups (Scheme 10).



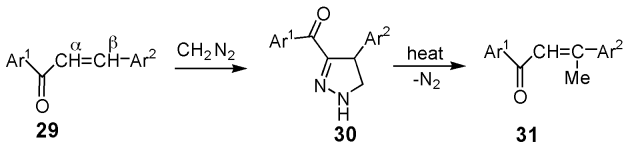
Aleksandrova *et al.* [33] prepared 4-aryl-3-(2-furyl)-2-pyrazolines (**28**) by the cycloaddition of 2-furyl analogues of chalcones **27** and diazomethane without the detection or isolation of the appropriate 1-pyrazoline isomers (Scheme 11).



27 **28**

R^1: H, Me; R^2: substituted phenyl, 2-furyl

The above examples (Schemes 8-11) unequivocally prove that there were several conflicting data concerning the structure of pyrazolines formed by the 1,3-dipolar cycloaddition of α,β-enones with diazomethane. We have reinvestigated the reaction of substituted chalcones and related α,β-unsaturated ketones **29** with diazomethane in order to establish unequivocally the structure of the resulting pyrazolines [34-36]. Compounds **29** were allowed to react with diazomethane in a mixture of anhydrous ethyl ether and methylene chloride or acetone at *ca*. 0° and the progress of the reaction was monitored by thin-layer chromatography (tlc). In the solution two new compounds were detected by tlc, one of which gradually disappeared and finally one spot was detected on the chromatogram when the starting α,β-enone was completely consumed. On the removal of the solvent a homogeneous product was obtained. Combined ultraviolet, infrared, and ^{1}H and ^{13}C nmr spectroscopic investigations unambiguously proved that the isolated product was the 3-aroyl-4-aryl-2-pyrazoline **30** in each case (Scheme 12) [34-36].



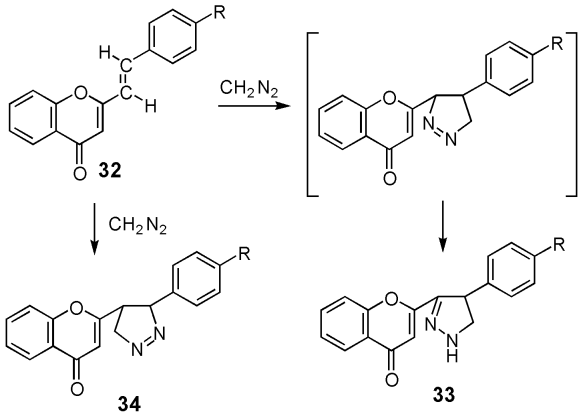
29 **30** **31**

Ar^1: substituted phenyl, 1-naphtyl, 2-naphthyl;
Ar^2: substituted phenyl, 1-naphtyl, 2-naphthyl, 3-chromonyl, 3-(2-chloro)quinolyl, 2-phenanthryl, 3-phenanthryl, 9-phenanthryl

Regiochemistry of this 1,3-dipolar cycloaddition should also be proven since the methylene part of the diazomethane can theoretically attack both the α and β carbon atom of the α,β-enone. On the basis of our comprehensive spectroscopic study, there was no question concerning the structure of the pyrazolines obtained in the course of our experiments. Nevertheless, we have corroborated the regioselectivity of this reaction by the thermal denitrogenation of the pyrazolines prepared. The isolated β-methyl-α,β-unsaturated ketones **31** unequivocally prove that the methylene part of the diazomethane attacked the β-carbon atom of the α,β-enone in the course of the cycloaddition (Scheme 12) [35].

On the basis of our experiences gained in the course of the study of the reaction of α,β-unsaturated ketones with diazomethane, it seemed expedient to investigate this 1,3-dipolar cycloaddition with related unsaturated compounds bearing a longer conjugated system than the α,β-enones. 2-Styrylchromones and cinnamylideneacetophenones appeard to be convenient substrates for this purpose.

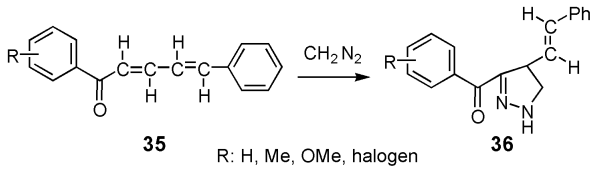
E-2-Styrylchromones **32** were allowed to react with diazomethane in a mixture of anhydrous diethyl ether and chloroform at room temperature and 4-aryl-3-(2-chromonyl)-2-pyrazolines **33** were obtained as major products. A minor component could also be detected by a careful chromatographic investigation of the crude reaction product. These minor components were isolated and proved to be 3-aryl-4-(2-chromonyl)-1-pyrazolines **34** on spectroscopic structure elucidation. It can be concluded from these results that the cycloaddition of the 2-styrylchromones and diazomethane is highly regioselective. The most part of the initially formed 4-aryl-3-(2-chromonyl)-1-pyrazolines spontaneously rearrange into their 2-pyrazoline isomers **33** which are isolated as the major product of the reaction. However, 1-pyrazolines as minor components **34** have also been isolated (Scheme 13) [37].



32 **34** **33**

R: H, Me, OMe, Cl

Recently we have studied the reaction of *E*,*E*-cinnamylideneacetophenones **35** with diazomethane which afforded 3-aroyl-4-styryl-2-pyrazolines **36** exclusively (Scheme 14) [38]. Therefore, it can be concluded that the 1,3-dipolar cycloaddition of these α,β,γ,δ-unsaturated ketones and diazomethane is similar to that of the related α,β-unsaturated ketones. Namely, the 1-pyrazolines formed in a completely regioselective cycloaddition spontaneously rearrange into their thermodinamycally more stable 2-pyrazoline isomers [38].



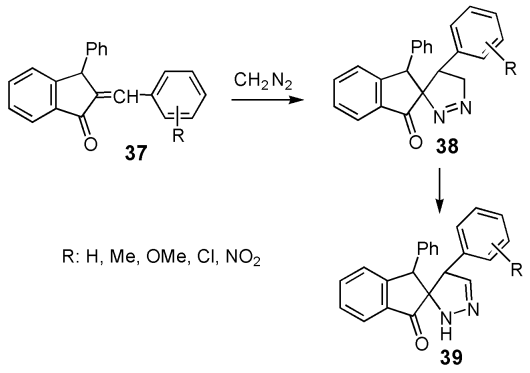
35 **36**

R: H, Me, OMe, halogen

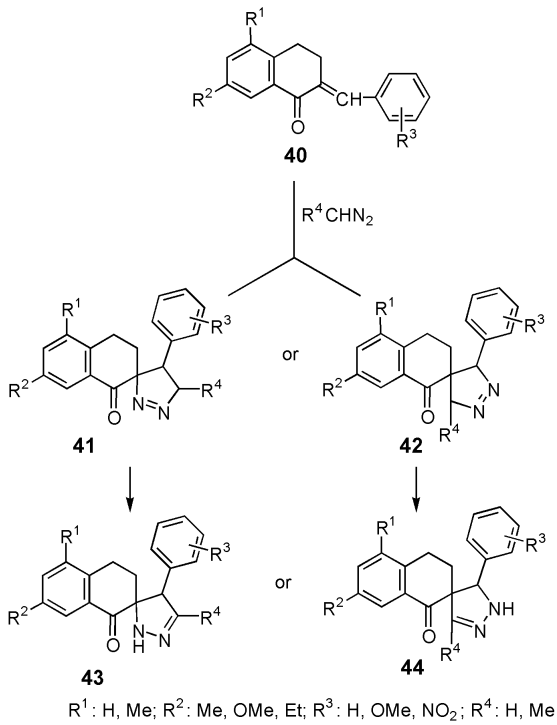
3.2. Reaction of Exocyclic α,β-Unsaturated Ketones and Diazoalkanes.

As shown in the preceding section, synthesis of 2-pyrazolines by the reaction of α,β-unsaturated ketones with diazoalkanes has been studied by several research groups [9,27-38]. However, 1,3-dipolar cycloadditions of diazoalkanes to exocyclic α,β-enones has received significantly less attention prior to our own work in this field.

The reaction of 2-arylidene-3-phenyl-1-indanones **37** with diazomethane performed by Mustafa and Hilmy in 1951 [39] can be considered as the first example of pyrazoline formation by the cycloaddition of an exocyclic α,β-unsaturated ketone and a diazoalkane. However, the authors were unable to establish whether their compounds were 1-pyrazolines **38** or 2-pyrazolines **39** (Scheme 15) [39].

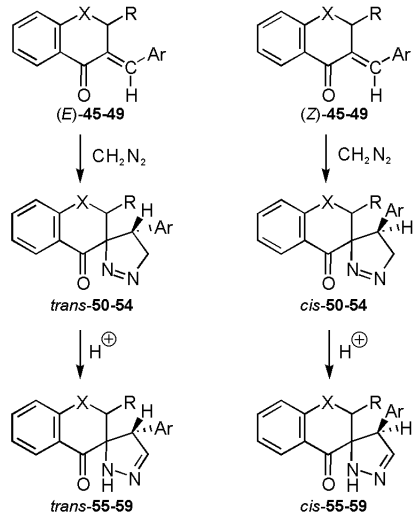


Reaction of 2-arylidene-1-tetralones **40** and diazomethane has been investigated by Fateen *et al*. [40,41]. They described the formation of pyrazoline isomers **41**-**44** (Scheme 16), but without spectroscopic measurements umambiguous structural assignment could not be performed.



Pijewska *et al*. [42,43] studied the reaction of 3-arylideneflavanones and diazomethane to yield pyrazolines. Unfortunately, neither the regiochemistry of this cycloaddition nor the stereochemistry of compounds synthesized were unambiguously established in their papers [42,43]. These very few literature reports prompted us to perform a detailed investigation of the 1,3-dipolar cycloadditions to a wide variety of exocyclic α,β-unsaturated ketones.

In order to elucidate the stereochemistry of this 1,3-dipolar cycloaddition, the (*E*)- and (*Z*)-isomers of 2-arylidene-1-tetralones **45**, 3-arylidenechromanones **46**, -1-thiochromanones **47**, -flavanones **48** and -1-thioflavanones **49** were allowed to react with diazomethane, the spiro-1-pyrazolines **50**-**54** were obtained exclusively (Scheme 17) [44-49].

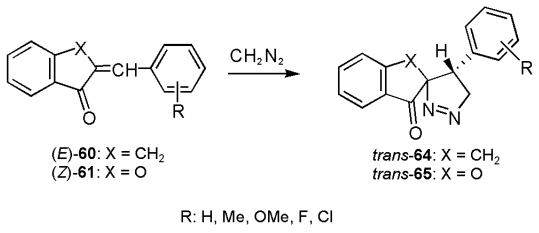


X: CH_2, O, S; R: H, Ph; Ar: substituted phenyl, 1-naphthyl, 2-naphthyl

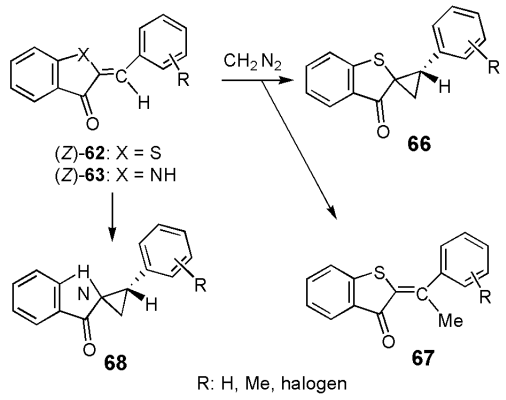
The structure and stereochemistry of compounds **50**-**54** have been elucidated by various nmr techniques. This detailed spectroscopic investigation unambiguously proved that the (*E*)-α,β-enones provided *trans*-spiro-1-pyrazolines *trans*-**50**-**54** and their (*Z*)-isomers gave the appropriate *cis*-spiro-1-pyrazolines *cis*-**50**-**54**. Therefore, it can be concluded that this 1,3-dipolar cycloaddition is stereospecific affording stereohomogeneous spiro-1-pyrazolines. The regiochemistry of this reaction should also be clarified. The ^{1}H nmr spectra proved a complete regioselectivity, *viz.* the carbon atom of the diazomethane is connected to the β-carbon atom of α,β-enones **45**-**49** [44-49]. This conclusion is corroborated by the fact that the thermal denitrogenation of spiro-1-pyrazolines synthesized by us provided β-methyl-α,β-enones in each case [50]. Their α-methyl-isomers have never been detected among the products of the thermal denitrogenation. These studies [44-49] also show that the regiochemistry supposed by Pijewska *et al*. [42,43] was incorrect.

It is noteworthy that our findings prove that, contrary to those results observed in the case of α,β-unsaturated ketones (*cf.* chapter 3.1.), 1-pyrazolines obtained from such exocyclic α,β-unsaturated ketones are stable compounds and do not isomerize spontaneously to the isomeric 2-pyrazolines. Therefore, this reaction cannot be used for the direct synthesis of 2-pyrazolines. However, the acid-catalyzed isomerization of such spiro-1-pyrazolines is an efficient method for the preparation of otherwise inaccessible spiro-2-pyrazolines. Therefore, we have converted spiro-1-pyrazolines **50-54** into spiro-2-pyrazolines **55-59** on treatment with trifluoroacetic acid in chloroform solution (Scheme 17) [45,46]. According to our detailed nmr spectroscopic investigations, the relative configuration was not changed in the course of this isomerization. Namely, *trans*-spiro-1-pyrazolines *trans*-**50-54** gave *trans*-spiro-2-pyrazolines *trans*-**55-59** and compounds *cis*-**50-54** yielded substances *cis*-**55-59** (Scheme 17). It should also be emphasized that the relative configuration of the starting α,β-enones **45-49** is retained both in the course of the 1,3-dipolar cycloaddition with diazomethane and during the acid-catalyzed isomerization of the spiro-1-pyrazolines into spiro-2-pyrazolines [44-49].

Other groups of substrates used for our cycloaddition experiments comprised of α,β-enones with a five-membered ring system, *viz.* (*E*)-2-arylidene-1-indanones **60**, (*Z*)-aurones **61**, (*Z*)-1-thioaurones **62** and (*Z*)-2-arylidene-2,3-dihydro-1*H*-indol-3-ones **63**. Compounds **60-63** were allowed to react with diazomethane and spiro-1-pyrazolines **64** and **65** were obtained from compounds **60** and **61** (Scheme 18) [51,52]. Structure elucidation based on nmr spectroscopic measurements revealed that the cycloaddition was stereospecific in the case of these groups of exocyclic α,β-unsaturated ketones as well. Both compounds **60** and **61** yielded *trans*-spiro-1-pyrazolines **64** and **65** as stereohomogeneous products as in the case of their six-membered homologues **45** and **46** (Scheme 18). Spiro-1-pyrazolines have been synthesized by the reaction of two 2-arylidene-1-indanones with diazomethane by Neudeck [53], but no mention is made of the stereochemistry of either the starting α,β-enones or the pyrazolines synthesized.



However, no pyrazoline type compound could even be detected in the crude reaction mixtures if (*Z*)-1-thioaurones **62** or (*Z*)-2-arylidene-2,3-dihydro-1*H*-indol-3-ones **63** were allowed to react with diazomethane under the same reaction conditions [51,52]. A spontaneous denitrogenation takes place almost immediately after the formation of the appropriate pyrazolines providing a mixture of cyclopropane derivatives **66** and β-methyl-α,β-enones **67** in the case of (*Z*)-1-thioaurones **62** (Scheme 19) [51]. The same reaction of the (*Z*)-2-arylidene-2,3-dihydro-1*H*-indol-3-ones **63** gave only cyclopropane type compounds **68** (Scheme 19) [51]. These experimental results prove that the 1,3-dipolar cycloaddition of diazomethane to compounds **62** and **63** cannot be utilized for the synthesis of pyrazolines owing to the instability of pyrazolines obtained from such α,β-enones.



4. Synthesis of 2-Pyrazolines by the Cycloaddition of Nitrile Imines with α,β-Enones.

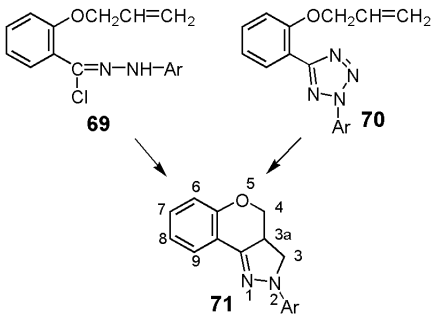
In the preceding chapter, the synthesis of 2-pyrazolines by the utilization of diazoalkanes as convenient nitrogen-containing 1,3-dipoles has been discussed. However, the reaction of diazoalkanes with unsaturated compounds gives 1-pyrazolines as primary products which either spontaneously convert to, or can be rearranged in a subsequent step into their corresponding 2-pyrazoline isomers. Another group of versatile nitrogen-containing reagents comprises the nitrile imines. 1,3-Dipolar cycloaddition of nitrile imines to dipolarophiles affords 2-pyrazolines in a one-step process. The concerted nature of the 1,3-dipolar cycloaddition of diazoalkanes and nitrile imines should be emphasized since this is the source of the complete stereoselectivity in the formation of stereohomogeneous pyrazolines in both cases.

Nitrile imines are readily available 1,3-dipoles generated *in situ* from stable precursors. There are several known procedures for the generation of these reagents. Since it is not an aim of this review to discuss the synthesis of nitrile imines in detail, only three procedures regularly utilized in the course of the synthesis of 2-pyrazolines will be discussed. Thermal denitrogenation of 2,5-disubstituted tetrazoles is exploited for the *in situ* generation of nitrile imines [54-56]. Another generally used procedure is based

on the dehydrohalogenation of hydrazide chlorides [54-58]. Lead tetraacetate oxidation of aldehyde hydrazones is also an opportunity for the generation of nitrile imines [59].

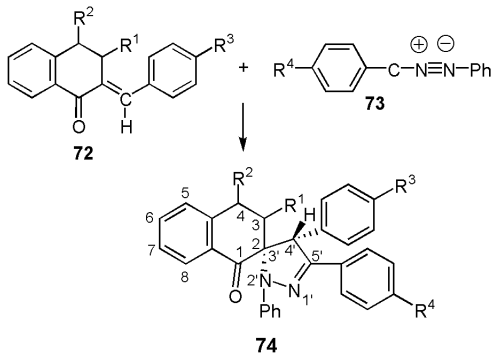
The synthesis of 2-pyrazolines by the 1,3-dipolar cycloaddition of unsaturated compounds and nitrile imines has featured in several excellent reviews [56,58,60] and a book [61]. Frontier molecular orbital calculations have also been performed for the evaluation of the selectivity of this 1,3-dipolar cycloaddition [62,63]. Since the synthesis of 2-pyrazolines by this reaction is well reviewed, the aim of this account is to present a selection of examples to illustrate the use of nitrile imines for this purpose.

The synthesis of tricyclic 2-pyrazolines by an intramolecular 1,3-dipolar cycloaddition of nitrile imines is well documented in the literature [64-76]. 2,3,3a,4-Tetrahydro-2-aryl-[1]benzopyrano[4,3-*c*]pyrazoles **71** have been prepared by the intramolecular 1,3-dipolar cycloaddition of nitrile imines generated either from 1-(*o*-allyloxyphenyl)-*N*-(arylhydrazidoyl) chloride **69** on treatment with triethylamine or by the irradiation of 2-aryl-5-(*o*-allyloxyphenyl)tetrazole **70** (Scheme 20) [69,70,76]. Various 2,3-disubstituted 2,3,3a,4-tetrahydro[1]benzopyrano[4,3-*c*]pyrazoles have also been synthesized by the utilization of nitrile imine intermediates [71-75].



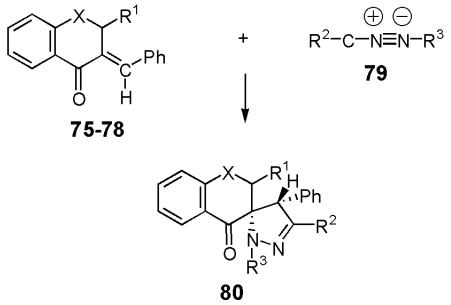
Spiro-2-pyrazolines **74** have been synthesized by Laude *et al*. [77] by the 1,3-dipolar cycloaddition of 2-arylidene-1-tetralones **72** with diarylnitrile imines **73** (Scheme 21). The structure and stereochemistry of compounds **74** have been elucidated by nmr spectroscopic measurements. These spectroscopic investigations revealed a regioselective and diastereoselective ring formation.

Various spiro-2-pyrazolines have been synthesized by Fisera and Lévai [78-80] by the 1,3-dipolar cycloaddition of (*E*)-2-benzylidene-1-tetralone (**75**), (*E*)-3-benzylidene-chromanone (**76**), -1-thiochromanone (**77**) and –flavanone (**78**). Compounds **75-78** were allowed to react with nitrile imines **79** generated *in situ* and the spiro-2-pyrazolines **80** were obtained (Scheme 22). Structure elucidation of spiro-2-pyrazolines **80** has been performed by a combination of



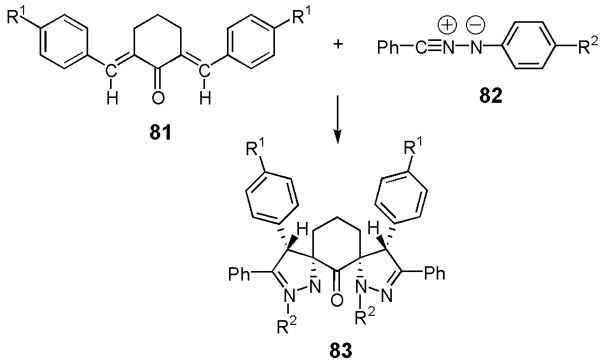
R^1: H, Me; R^2: H, Me, Et, iPr, tBu; R^3: H, Me; R^4: H, Me, OMe

nmr techniques. The stereochemistry of **80** confirms a completely regio- and diastereoselective cycloaddition reaction.



X: CH_2, O, S; R^1: H, Ph;
R^2: 4-nitrophenyl, 5-nitro-2-furyl; R^3: Me, Ph

A recent development in this field is the synthesis of 1,3,4,8,10,11-hexaaryl-1,2,8,9-tetraazadispiro[4.1.4.3]-tetradeca-2,9-dien-6-ones **83** by the reaction of 2,6-diarylidene-cyclohexanones **81** with nitrile imines **82** (Scheme 23) [81]. The reaction is regioselective, but provides a mixture of diastereomers of compound **83**.



R^1: H, Me, OMe, F, Cl; R^2: H, Me

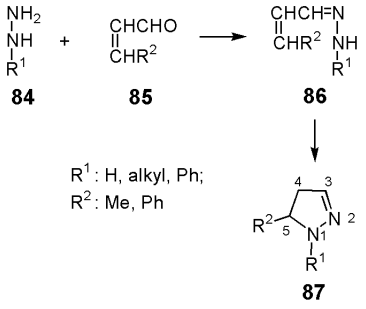
To close this chapter, one can conclude that the *in situ* generated nitrile imines are convenient and versatile nitrogen-containing reagents for the stereoselective formation of 2-pyrazolines by means of their 1,3-dipolar cycloaddition

with unsaturated compounds. Since such 2-pyrazolines can be easily oxidized to the corresponding pyrazoles, otherwise inaccessible pyrazoles may become available *via* these chemical transformations.

5. Synthesis of 2-Pyrazolines by the Reaction of α,β-Unsaturated Aldehydes and Ketones with Hydrazines.

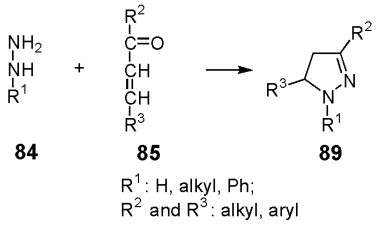
5.1. Reaction of α,β-Unsaturated Aldehydes with Hydrazines.

In the introduction we have already mentioned that the first reactions of α,β-enones and hydrazine derivatives have been conducted as early as the late nineteenth century and in the first decades of the twentieth century [1-3,82-84]. α,β-Unsaturated aldehydes **85** afforded hydrazones **86** on reaction with hydrazines **84** (Scheme 24). These aldehyde hydrazones **86** yielded 2-pyrazolines **87** on an acid-catalyzed ring closure (Scheme 24). The addition of the NH moiety to the C=C double bond of hydrazones **86** is supposed to be a rate-controlling step in the formation of 2-pyrazolines **87** (Scheme 24). Electronic structure, stereochemistry and solubility of the hydrazones may influence the ring closure reaction affording 2-pyrazolines **87**.



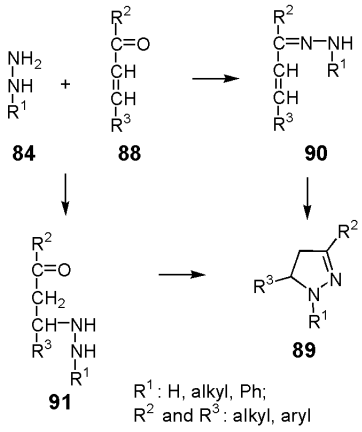
5.2. Preparation of 2-Pyrazolines by the Reaction of Chalcones and Related α,β-Unsaturated Ketones with Hydrazines.

The reaction of chalcones and related α,β-unsaturated ketones **88** with hydrazines **84** is probably the most popular procedure for the synthesis of 2-pyrazolines **89** (Scheme 25). This reaction can be conducted under various conditions.



The most commonly used method is the reaction of compounds **84** and **88** in acetic acid solution to prepare 2-pyrazolines **89** in high yield (Scheme 25) [82,83,85-94]. This method is used either with or without the isolation of the hydrazone intermediate **90**. Another opportunity for the reaction of α,β-unsaturated ketones **88** and hydrazines **84** under acid-catalyzed conditions is the use of hydrazine hydrochloride in hot alcoholic or dimethylformamide solution [95-97]. Synthesis of 2-pyrazolines **89** can also be achieved under alkaline conditions by using pyridine as catalyst in ethanolic solution [98] or as solvent [99]. In some cases the two reactants were refluxed in alcoholic solution without catalyst to provide 2-pyrazolines **89** [84,100,101].

The mechanism of the above discussed reactions affording 2-pyrazolines has been studied under various reaction conditions. On the basis of numerous experimental findings, it has been concluded that the reaction of α,β-enones **88** with hydrazines **84** yields 2-pyrazolines **89** *via* hydrazone intermediates **90** under acidic conditions [86,93,102-104] (Scheme 26). However, if piperidine was used as the catalyst, the β-hydrazinoketones **91** were formed as intermediates, the ring closure of which gave 2-pyrazolines **89** [93] (Scheme 26).



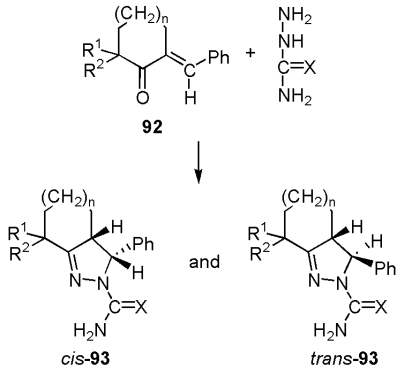
To close this chapter, it can be stated that this simple and versatile procedure has been utilized for the synthesis of numerous 2-pyrazoline derivatives.

5.3. Reaction of Exocyclic α,β-Enones with Hydrazines.

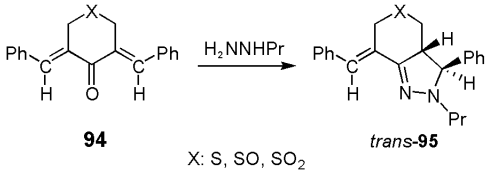
Exocyclic α,β-unsaturated ketones are convenient starting materials for the synthesis of 2-pyrazolines as shown in the preceding sections. Such α,β-enones also readily react with hydrazines to afford bicyclic or tricyclic 2-pyrazolines.

One group of the exocyclic α,β-unsaturated ketones used for this purpose comprises 2-arylidenecycloalkanones, various diarylidenecycloalkanones, and their thia- and aza-analogues. 2-Pyrazolines have been synthesized *e.g.* from 2-alkylidene-, 2-arylidenecycloalkanones and 2,6-diarylidenecyclohexanones by their reaction with hydrazine [105-107].

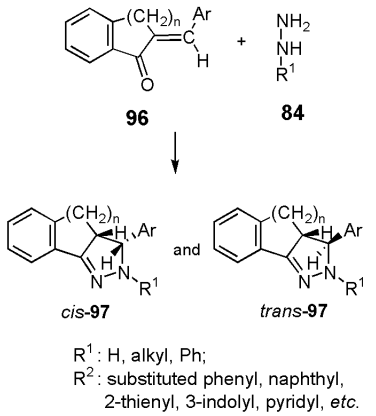
Lóránd *et al*. [108] investigated the synthesis of bicyclic 2-pyrazolines **93** by the reaction of benzylidenecycloalkanones **92** with hydrazine derivatives like semicarbazide and thiosemicarbazide in refluxing ethanolic solution using hydrochloric acid as the catalyst. This reaction afforded a *cis/trans* mixture of the corresponding bicyclic 2-pyrazolines which were separated by column chromatography. The relative configuration and conformation of compounds *cis*-**93** and *trans*-**93** have been determined by nmr spectroscopy and X-ray diffraction analysis (Scheme 27). Similar bicyclic 2-pyrazolines have been synthesized by Husebye *et al*. [109] by the reaction of 2,6-bis(ferrocenylmethylene)cyclohexanone and methylhydrazine.



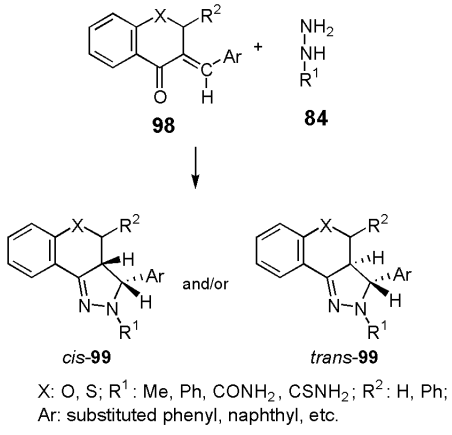
Bicyclic 2-pyrazolines **95** have been prepared by the reaction of the 4-thia-analogues **94** of 2,6-dibenzylidenecyclohexanone with *n*-propylhydrazine in hot methanol (Scheme 28) [110,111]. *Trans* relative configuration of the chirality centres of compounds **95** was deduced from a detailed nmr spectroscopic investigation. Reaction of the 4-aza-analogues of the 2,6-diarylidenecyclohexanones with hydrazines provided similar bicyclic 2-pyrazolines [112].



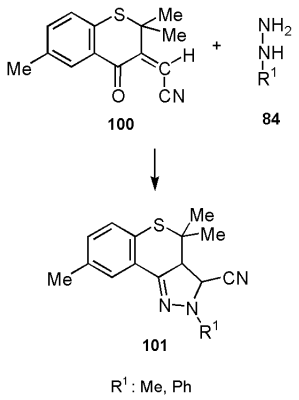
The reaction of 2-arylidenebenzocyclanones **96** and hydrazines has been studied by several research groups [113-123]. The hydrazines were reacted with 2-arylidene-1-indanones (**96**, n=1), 2-arylidene-1-tetralones (**96**, n=2) and 2-arylidene-1-benzosuberones (**96**, n=3) under various reaction conditions to afford the tricyclic 2-pyrazolines **97** (Scheme 29). In many cases, the appropriate α,β-enone **96** and hydrazine were refluxed for several hours in methanolic or ethanolic solution to afford 2-pyrazolines **97** in good yields [114,115,118,120,123]. Alternatively, the two reactants may be reacted under acid-catalyzed conditions. One drawback of this method is that *cis/trans* mixtures of the tricyclic 2-pyrazolines are formed (Scheme 29) [116,119,121]. However, the *cis/trans* diastereomers can be separated and isomerized into each other [122]. Lévai *et al*. [117] have studied the reaction between 2-benzylidene-1-tetralone (**96**, n=2) and hydrazines in hot pyridine from which the *trans*-2-pyrazolines *trans*-**97** were obtained in good yield in a completely diastereoselective ring formation (*cf.* Scheme 29).



Synthesis of tricyclic 2-pyrazolines **99** has also been conducted by the reaction of 3-arylidenechromanones (**98**, X=O) and their thio analogues (**98**, X=S) and hydrazines either in hot ethanol [42] or in refluxing pyridine solution [117,124-126]. If the reaction was performed in alcoholic solution, a *cis/trans*-mixture of 2-pyrazolines were obtained [42]. When pyridine was used as solvent, stereohomogeneous tricyclic *trans*-2-pyrazolines *trans*-**99** were obtained (Scheme 30) [117,124-126]. However, if the same reaction was undertaken in hot ethanol in the presence of hydrochloric acid, the *cis*-compounds **99** (*cf*. Scheme 30) were obtained as major products, but *trans*-**99** as a minor product could also be detected in the crude reaction mixture and has been isolated in some cases [127,128].

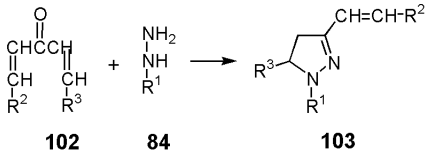


In a more recent report, tricyclic 2-pyrazolines **101** were synthesized by the reaction of 3-cyanomethylene-2,2,6-trimethyl-1-thiochromanone (**100**) with methyl- and phenylhydazine in refluxing ethanol (Scheme 31) [129].



5.4. Synthesis of 2-Pyrazolines by the Reaction of Diarylideneacetones and Hydrazines.

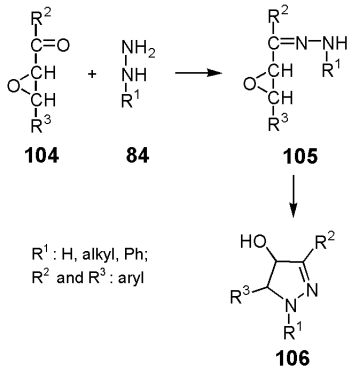
The reaction of diarylideneacetones **102** and hydrazines **84** yielded 2-pyrazolines **103** with unsaturated side chain (Scheme 32) [130-136]. It is notable that during the formation of 2-pyrazolines **103** one of the α,β-unsaturated moieties of the starting materials participates and the other double bond is almost without influence on the reaction. On this basis it can be concluded that the reaction of hydrazines with α,β-enones and diarylideneacetones is the same. The presence of the unsaturated side chain may render such 2-pyrazolines convenient building blocks for more elaborately substituted compounds.



6. Synthesis of 2-Pyrazolines by the Reaction of α,β-Epoxyketones with Hydrazines.

α,β-Epoxyketones are well known versatile building blocks used for a wide variety of chemical transformations making possible the synthesis of organic compounds with quite complex structures. Among the α,β-epoxyketones the chalcone epoxides are especially important and useful compounds. Their first syntheses were conducted as early as 1916 [137-139]. Procedures used for this purpose were based on the alkaline-catalyzed reaction of ω-haloacetophenones with substituted benzaldehydes. Some years later, Weitz and Scheffer invented the alkaline hydrogen peroxide epoxidation of chalcones which is a widely explored simple and convenient procedure.

The oxirane ring of chalcone epoxides can be easily opened with nucleophilic reagents, a transformation which may be utilized for the preparation of nitrogen-containing heterocyclic compounds. When hydrazines **84** are used as nucleophiles, 4-hydroxy-2-pyrazolines **106** are obtanined *via* the hydrazones **105**, formed as the initial product from chalcone epoxides **104** (Scheme 33) [137-139,141-145].

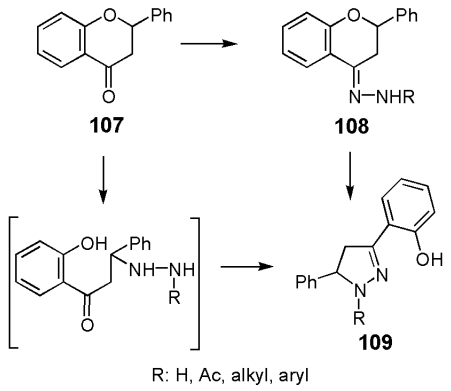


Stereochemical studies have revealed that the reaction of *trans*-chalcone epoxides with hydrazine (**84**, R^1=H) affords *trans*-3,5-diaryl-4-hydroxy-2-pyrazolines as the sole products in a completely stereoselective reaction [142,143].

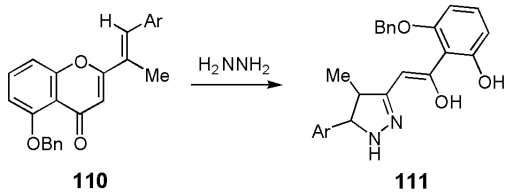
7. Reaction of Chromanone and Chromone Derivatives with Hydrazines.

Reaction of 2-phenylchromanones (flavanones) **107** and hydrazines has been thoroughly studied by Kállay *et al*. [146-149] and in other laboratories [150,151]. The experimental results accumulated to date prove that, among the different nitrogen-containing reaction products, 2-pyrazolines **109** may also be present depending on the choice of reaction conditions (Scheme 34). An alkaline medium has proved to be beneficial for pyrazoline formation. According to the assumption of Kállay *et al.* [146-149], pyrazoline formation may proceed through the corresponding flavanone hydrazone **108** or *via* the hydrazinolysis of the heteroring of the flavanone (Scheme 34). However, since 2-pyrazolines obtained in this way are identical to those synthesized by the reaction of hydrazines with 2'-hydroxychalcones, the precursor for the synthesis of the appropriate flavanones, this procedure cannot be considered as an efficient method for the preparation of 2-pyrazolines.

Reaction of chromones with hydrazines usually affords pyrazoles instead of pyrazolines [152-155]. Though the reaction of some 2-styrylchromones **110** and hydrazine



affords 2-pyrazolines **111**, but only as by-products in very low yields (4-15%) (Scheme 35). The major products being the pyrazoles.



8. Closing Remarks.

In the introduction, we have summarized the early strategies employed for the synthesis of pyrazolines. In this review article we have compiled and discussed synthetic routes to 2-pyrazolines. The reason for this is, that the 2-pyrazolines comprise the largest group among the different pyrazoline isomers. Our aim was to discuss each procedure *via* adequate examples in order to show the major benefits of a particular method. Therefore, in the case of certain routes we have not included all of the published papers, instead we have used only those examples considered to be the most characteristic for a method. Literature data published to March 2001 have been included as references to help the reader to find original papers for the synthesis of a particular compound or to find an experimental procedure.

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