Chemistry of Heterocyclic Compounds, Vol. 33, No. 6, 1997

SYNTHESIS OF PYRAZOLINES BY THE REACTIONS OF α,β-ENONES WITH DIAZOMETHANE AND HYDRAZINES (REVIEW)

Albert Lévai

The first representatives of pyrazolines were synthesized in the last century. These nitrogen-containing heterocyclic compounds became important in the development of different bioactive substances. For this reason, various procedures have been worked out for their synthesis. In the present article we summarize those synthetic methods providing 1- or 2-pyrazolines by the reactions of α,β-unsaturated ketones with diazomethane or hydrazine derivatives.

INTRODUCTION

It was more than a hundred years ago that Fischer and Knövenagel described the synthesis of a pyrazoline by the reaction of phenylhydrazine and acrolein [1]. This report is probably the first example of pyrazoline formation by the reaction of an α,β-unsaturated carbonyl compound with a hydrazine derivative. Formation of 1-phenyl-2-pyrazoline in this way was corroborated by Auwers et al. [2, 3]. Following these pioneering investigations, the reaction of α,β-enones with hydrazines made possible the preparation of innumerable pyrazolines.

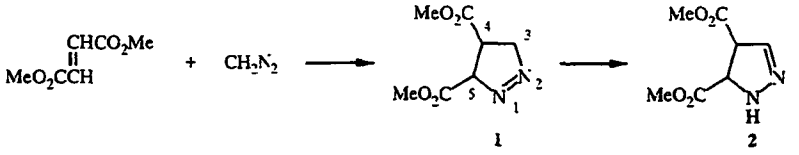
As far as pyrazoline formation is concerned, another milestone was the discovery of the reaction of diazoalkanes with α,β-unsaturated carboxylic acids [4-7] and α,β-enones [8, 9] in the early twentieth century. Especially the diazomethane as a nitrogen source made possible the preparation of numerous 1-pyrazolines which could then be converted into their corresponding 2-pyrazoline isomers or cyclopropanes on denitrogenation [10-14].

Synthesis of pyrazolines has been also stimulated by the fact that some of their derivatives were found to possess important bioactivities. Especially their antimicrobial [15], immunosuppressive [16] and central nervous system activity [17] should be emphasized. Although pyrazolines are useful substances in drug research and are well-known five-membered nitrogen-containing heterocyclic compounds, a comprehensive review on their synthesis was published thirty years ago [18]. The aim of the present article is, therefore, to summarize the results of pyrazoline syntheses gained mainly during the last three decades.

SYNTHESIS OF PYRAZOLINES BY THE REACTION OF α,β-UNSATURATED KETONES WITH DIAZOMETHANE

Diazomethane was first synthesized by Pechmann in 1894 from N-nitrosourethane by reaction with potassium hydroxide. The diazomethane afforded then a pyrazoline-type compound on the reaction with dimethyl fumarate [19]. It also turned out that Pechmann correctly anticipated the mechanism of this reaction, viz. that the primary product of this cycloaddition is 1-pyrazoline (**1**) which then spontaneously isomerizes into the thermodynamically more stable 2-pyrazoline isomer (**2**) by 1,3-H shift (Scheme 1).

Scheme 1



Department of Organic Chemistry, Kossuth Lajos University, Egyetem ter I, H 4010 Debrecen, Hungary. Published in Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 747-759, June, 1997. Original article submitted March 14, 1997.

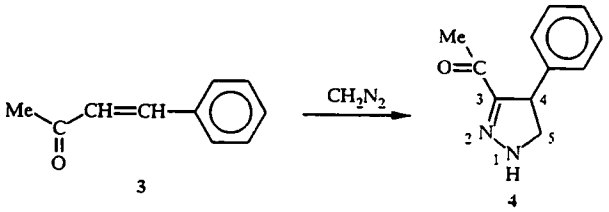
0009-3122/97/3306-0647$18.00

Although various diazoalkanes are available for the preparation of pyrazolines because of their high reactivity, diazomethane is mainly used for this purpose. Several anomalies have also been reported concerning the synthesis of pyrazolines by using diazoalkanes [20-23]. One common anomaly is the formation of pyrazole as a result of either an elimination reaction or oxidation of the initially formed pyrazoline by the cycloaddition of the unsaturated compound and the diazoalkane.

Reaction of Diazomethane with Chalcones and Related α,β-Enones

Probably the first example for the preparation of a pyrazoline by the reaction of an α,β-unsaturated ketone with a diazoalkane was published by Azzarello as early as 1906 [24]. Formation of 3-acetyl-4-phenyl-2-pyrazoline (**4**) was observed on the reaction of benzalacetone (**3**) with diazomethane in anhydrous ether (Scheme 2). This reaction was repeated later by Smith and Howard [25] and by Raju and Rao [26] who confirmed Azzarello's assumption [24].

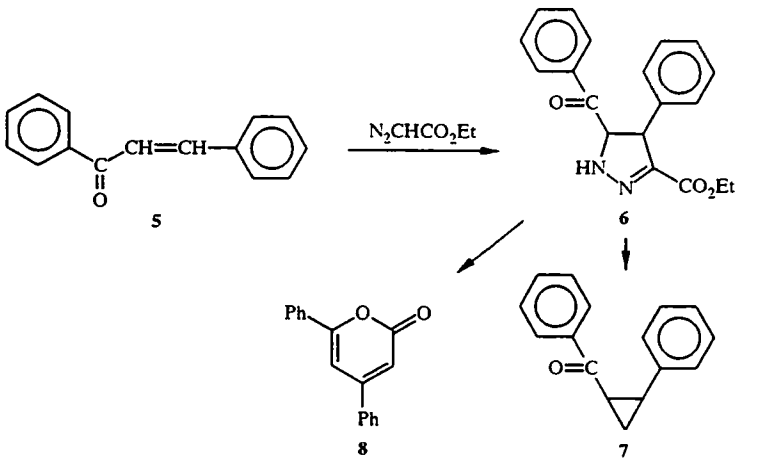
Scheme 2



3 4

Another early investigation of pyrazoline synthesis by the reaction of an α,β-unsaturated ketone with a diazoalkane was performed by Kohler and Steele [8]. Chalcone **5** was allowed to react with ethyl diazoacetate to obtain pyrazoline derivative **6** which was supposed to give a cyclopropane-type compound **7** and pyrone **8** on thermal denitrogenation (Scheme 3). But because of lack of an unambiguous structure elucidation of the pyrazoline prepared, one cannot judge which pyrazoline isomer was actually obtained in the reaction performed [27].

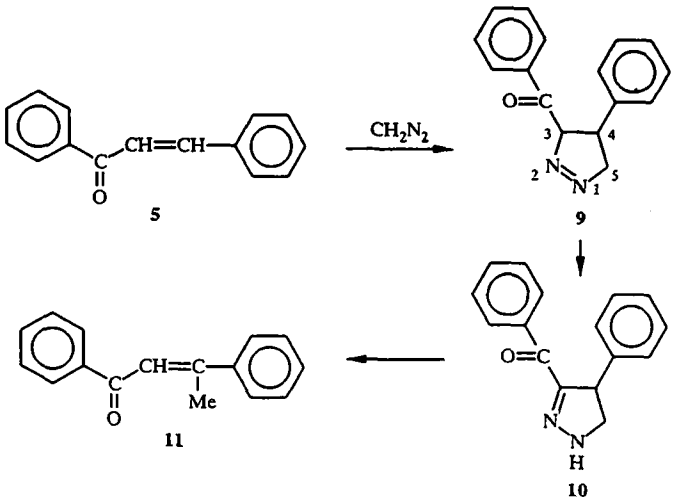
Scheme 3



5 6 7 8

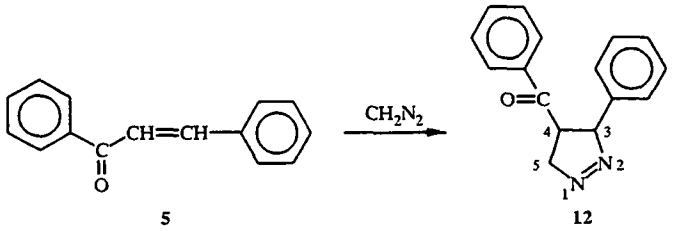
The reaction of chalcone **5** with diazomethane was first investigated by Smith and Pings [9], and 3-benzoyl-4-phenyl-1-pyrazoline (**9**) was obtained as a primary product which was then converted into 3-benzoyl-4-phenyl-2-pyrazoline (**10**) on gentle heating. Compound **10** yielded β-methylchalcone **11** on thermal denitrogenation (Scheme 4).

Scheme 4



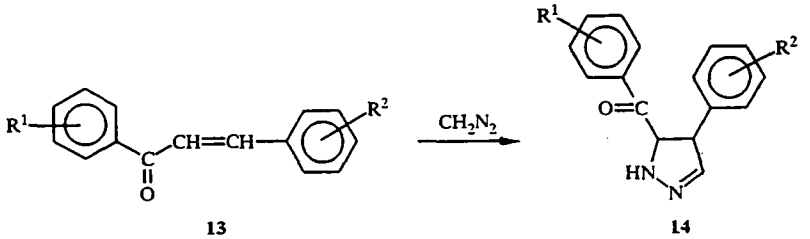
Later, Ghate et al. [28] assumed that this reaction of chalcone **5** gave 4-benzoyl-3-phenyl-1-pyrazoline (**12**) (Scheme 5), but on the basis of the melting point (132°C) published by them the product was probably 3-benzoyl-4-phenyl-2-pyrazoline (**10**) (cf. Scheme 4). No spectral data were provided to prove the assumed structure of their pyrazoline.

Scheme 5



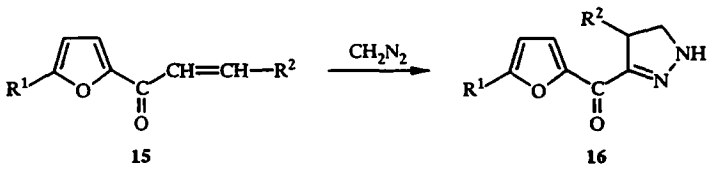
Mustafa and Fleifel [29], as well as Sayed and Kjosen [30], studied the reaction of variously substituted chalcones **13** with diazomethane but, probably because of the misinterpretation of the ^{1}H NMR spectra, Sayed and Kjosen assumed that the reaction led to the formation of 5-benzoyl-4-phenyl-2-pyrazolines (**14**). The formation of these pyrazoline isomers had been previously postulated by Mustafa and Fleifel [29] (Scheme 6) as well.

Scheme 6



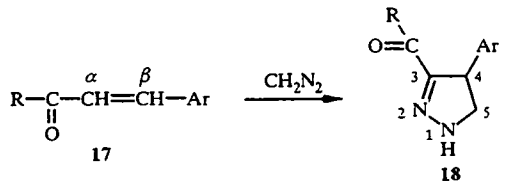
Starting with furyl analogues of chalcones **15** Aleksandrova et al. [31] synthesized 4-aryl-3-(2-furyl)-2-pyrazolines (**16**) without isolation or detection of the corresponding 1-pyrazoline isomers (Scheme 7).

Scheme 7



All these examples show unequivocally that there were many conflicting literature data concerning the synthesis of pyrazolines by the reaction of α,β-enones and diazoalkanes until about the late seventies. This situation prompted us to reinvestigate this reaction with a series of substituted chalcones and related α,β-unsaturated ketones **17** [32-34]. Substrates **17** were allowed to react with diazomethane in a mixture of either anhydrous ether and acetone or anhydrous ether and methylene chloride at 0°C, and the progress of the reaction was monitored by thin-layer chromatography (TLC). Such monitoring revealed the presence of two new substances in the reaction mixture, one of which gradually decreased and finally one spot was observed on the chromatogram. After the removal of the solvent, the residue was generally crystallized from methanol to obtain a homogeneous product, the structure of which was elucidated by spectroscopic methods. The detailed UV, IR, and ^{1}H and ^{13}C NMR spectroscopic investigations proved unequivocally that the isolated product was 3-acyl-4-aryl-2-pyrazoline (**18**) in each case [32-34] (Scheme 8).

Scheme 8



The reaction of α,β-unsaturated ketones with diazoalkanes can theoretically lead to two kinds of 1-pyrazoline (**A** and **B**) depending on whether the terminal nitrogen atom is connected to the α- or β-carbon atom of the α,β-enone in question. These 1-pyrazolines can then be rearranged into various pyrazoline isomers (**C**–**J**) outlined in Scheme 9. Structure elucidation of the product of the cycloaddition means, therefore, that the actual isomer should be chosen from the theoretically possible ten structures. By using combined ^{1}H and ^{13}C NMR spectroscopic measurements [32-34] eight structures can be unambiguously excluded, and only **C** and **G** isomers should be taken into account and differentiated. This differentiation cannot be performed by NMR spectroscopic measurements alone. However, both IR and UV spectra of **C** and **G** isomers should be characteristically different owing to the presence of conjugated or non-conjugated carbonyl group in the molecule. The IR carbonyl band measured between 1605 and 1632 cm^{-1} revealed the presence of a conjugated carbonyl group, proving the **C** structure. This conclusion was corroborated by the two characteristic UV bands at about 330 and 250 nm indicating the presence of the O=C(R)–C=N-chromophore.

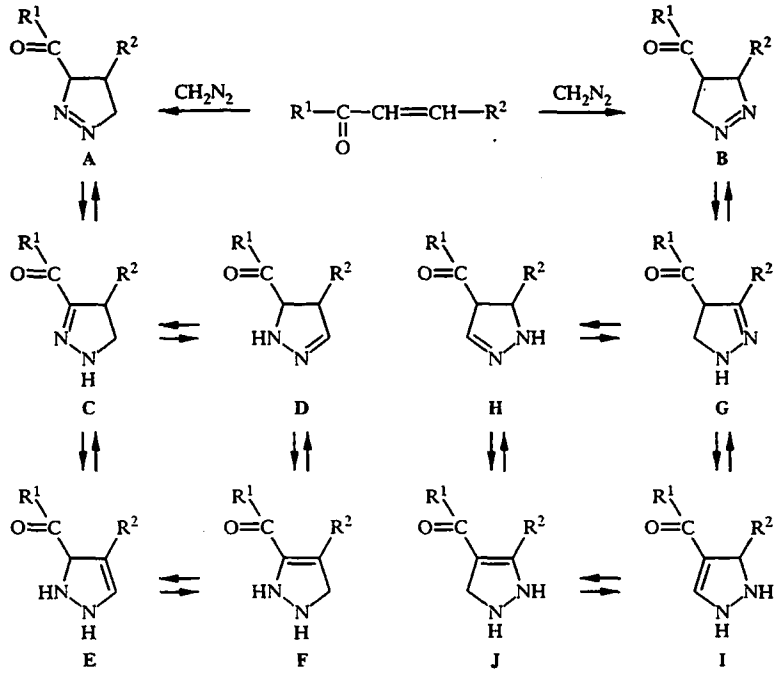
In summary, it can be stated that the cycloaddition of α,β-enones with diazomethane leads to the formation of such 1-pyrazolines where the methylene unit of diazomethane is connected to the β-carbon atom of the α,β-enone (A), and the compound then spontaneously isomerizes into the thermodynamically more stable 2-pyrazoline isomer (**C**) which has been the only isolable product at least in the cases and reaction conditions investigated so far.

Reaction of Diazomethane with Exocyclic α,β-Unsaturated Ketones

As described in the preceding section, the synthesis of pyrazolines by the reaction of chalcones and related α,β-enones with diazomethane has been investigated by several laboratories. However, a similar reaction of the so-called exocyclic α,β-unsaturated ketones and diazomethane affording spiropyrazolines received less attention prior to our own studies.

Mustafa and Hilmy [35] synthesized spiro-1-pyrazolines by the reaction of 2-arylidene-3-phenyl-1-indanones and diazomethane. Pijewska et al. [36, 37] investigated the cycloaddition of 3-arylideneflavanones and diazomethane to obtain spiropyrazolines. However, neither the regiochemistry of this reaction nor the stereochemistry of the compounds prepared have been unequivocally established in their papers [36, 37]. All these facts prompted us to perform a detailed study of the 1,3-dipolar cycloaddition of these α,β-enones and diazomethane.

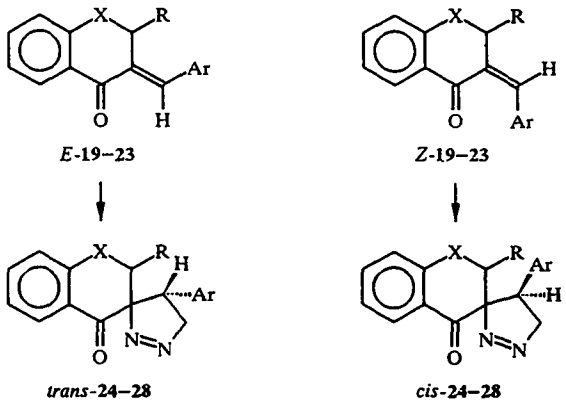
Scheme 9



Reaction of Diazomethane with Exocyclic α,β-Unsaturated Ketones

Both *E* and*Z* isomers of 2-arylidene-1-tetralones (**19**), 3-arylidene-chromanones (**20**), -1-thiochromanones (**21**), -flavanones (**22**) and -1-thioflavanones (**23**) were allowed to react with diazomethane to afford spiro-1-pyrazolines **24-28** (Scheme 10) [38-40]. The structure and stereochemistry of spiro-1-pyrazolines **24-28** have been elucidated by NMR spectroscopic measurements. All ^{1}H and ^{13}C NMR signals have been assigned by the combined use of various one-dimensional NMR methods. The relative configuration of the C-3 and C-4 chirality centers has been determined mainly by means of one-dimensional NOE difference measurements. These data can also be used, at the same time, for the differentiation of the *cis*- and *trans*-isomers of these spiro-1-pyrazolines. Thus, it can be concluded that this reaction is regio- and stereoselective affording trans-spiro-1-pyrazolines *trans*-**24-28** from *E*-α,β-enones *E*-**19-23** and *cis*-spiro-1-pyrazolines *cis*-**24-28** from compounds *Z*-**19-23** (Scheme 10).

Scheme 10



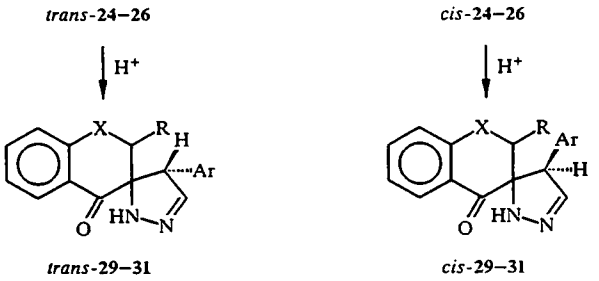
19, 24 R = H, X = CH_2; 20, 25 R = H, X = O; 21, 26 R = H, X = S;
22, 27 R = Ph, X = O; 23, 28 R = Ph, X = S

Consequently, this reaction is a completely stereoselective one-step process providing stereohomogeneous products as shown by Scheme 10. Conformational analysis of spiro-1-pyrazolines **24-28** has been also performed, and it can be concluded that the six-membered ring adopts a halfchair while the five-membered pyrazoline ring may adopt an envelope conformation [38-40].

As described in the previous section, 3-acyl-4-aryl-1-pyrazolines prepared by 1,3-dipolar cycloaddition of α,β-enones with diazomethane spontaneously isomerize into the thermodynamically more stable 2-pyrazolines. However, spiro-1-pyrazolines **24-28** are very stable compounds. Such an isomerization is, on the other hand, a convenient procedure for the preparation of spiro-2-pyrazolines which cannot be obtained directly. For this reason, the acid-catalyzed isomerization of the spiro-1-pyrazolines **24-28** synthesized by us has been investigated. It turned out that cis-spiro-1-pyrazolines (*cis*-**24-26**) can readily isomerize into *cis*-spiro-2-pyrazolines (*cis*-**29-31**) in one day at room temperature [40], whereas similar acid-catalyzed isomerization of their *trans*-isomers (*trans*-**24-26**) was not complete even in one month at room temperature. Nonetheless, this is the only procedure to prepare this type of spiro-2-pyrazolines from exocyclic α,β-enones (Scheme 11). It should be emphasized that the relative configuration of the starting material is retained during this isomerization. Because of denitrogenation as a competing reaction, a similar isomerization of spiro-1-pyrazolines **27** and **28** obtained from 3-arylideneflavanones **22** and their thio analogues **23** was unsuccessful.

To close this section, it should be mentioned that Pijewska et al. [36, 37] described the reaction of some 3-arylideneflavanones **22** and diazomethane

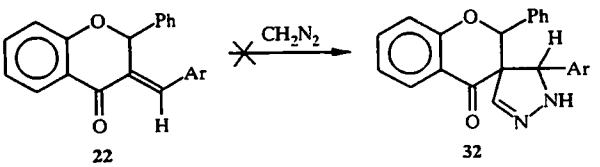
Scheme 11



29 X = CH_2; 30 X = O; 31 X = S

affording the spiro-2-pyrazolines **32**, where the methylene moiety of the diazomethane is connected to the α-carbon atom of the α,β-enone (Scheme 12). On the basis of our detailed spectroscopic investigations concerning the structures of the reaction products of 3-arylideneflavanone and diazomethane [38-40], it appears that the conclusion of Pijewska et al. [36, 37] is wrong and may result from a misinterpretation of the ^1H NMR spectra or from neglect of other spectroscopic measurements necessary for the structure elucidation. These compounds should actually be spiro-2-pyrazolines obtained by isomerization of the other regioisomer spiro-1-pyrazoline, where the methylene group is connected to the β-carbon atom.

Scheme 12



22 32

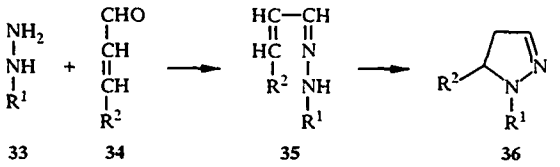
SYNTHESIS OF PYRAZOLINES BY THE REACTION OF α,β-ENONES AND HYDRAZINES

Reactions of α,β-Unsaturated Aldehydes with Hydrazines

As described in the Introduction, the first reactions of hydrazines **33** with α,β-unsaturated carbonyl compounds to form pyrazolines were performed in the late nineteenth and early twentieth centuries [1-3]. One group of such carbonyl com-

pounds was the α,β-unsaturated aldehydes (**34**) which gave hydrazones **35** on reactions with hydrazines [2, 3, 41-43]. Hydrazones **35** can then be easily converted into 2-pyrazolines **36** on treatment in acidic media (Scheme 13). The hydrazone-type intermediates were not isolated in each case, but they were assumed to be the primary reaction products of various α,β-unsaturated aldehydes and hydrazines. As a rate-controlling step in the pyrazoline formation, the addition of the NH group to the carbon–carbon double bond of hydrazones **35** was considered. The solubility, stereochemistry, and electron distribution of hydrazones may influence this ring closure reaction providing 2-pyrazolines [18].

Scheme 13

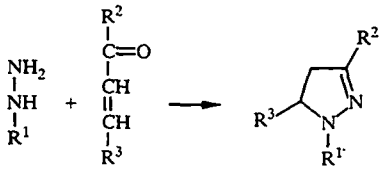


33 **34** **35** **36**

Preparation of 2-Pyrazolines by the Reaction of α,β-Unsaturated Ketones with Hydrazines

The most frequent synthesis of 2-pyrazolines is based on the reaction of α,β-unsaturated ketones (**37**) with hydrazines **33** under various reaction conditions (Scheme 14).

Scheme 14

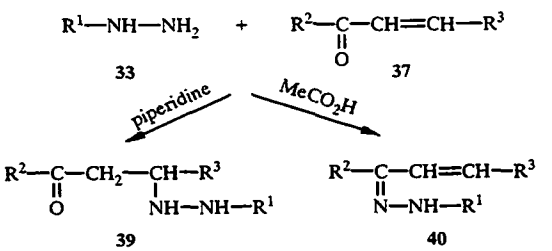


33 **37** **38**

Reaction of these two starting materials in acetic acid with or without the isolation of the intermediate hydrazone is a commonly used efficient procedure to prepare 2-pyrazolines **38** in high yields [44-52]. Hydrazines and α,β-unsaturated ketones have also been allowed to react in a hot alcohol solution [41, 53-55] or in a boiling mixture of benzene with ethanol [56]. Reaction of α,β-unsaturated ketones with phenylhydrazine in refluxing pyridine afforded 2-pyrazolines as well [57].

The mechanism of these reactions providing 2-pyrazolines has also been investigated under various reaction conditions. On the basis of numerous experimental results, it can be concluded that the reaction of α,β-unsaturated ketones **37** and hydrazines **33** in acidic medium leads to 2-pyrazolines via hydrazones as intermediates [44, 52, 58]. However, in the presence of piperidine, Michael addition takes place providing β-hydrazinoketones **39** instead of hydrazones **40** formed from the same starting materials in acetic acid (Scheme 15) [59].

Scheme 15

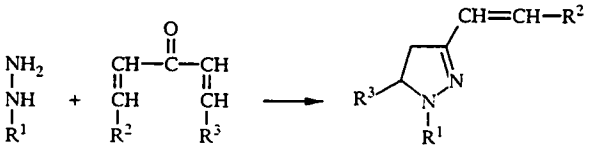


33 **37** **39** **40**

Reaction of Dibenzylideneacetones with Hydrazines

The reaction of hydrazines **33** has also been investigated with ketones possessing more than one double bond conjugated with the carbonyl group (compounds 41) [60-64]. Such reactions provided 2-pyrazolines **42** (Scheme 16) similarly to those obtained by the reactions of hydrazines **33** with α,β-unsaturated ketones **37** (cf. Scheme 14). Thus, the formation of 2-pyrazolines is based mainly on one of the α,β-unsaturated moieties of the substrate, and the other parts of the molecule have almost no influence on the result of the reaction.

Scheme 16

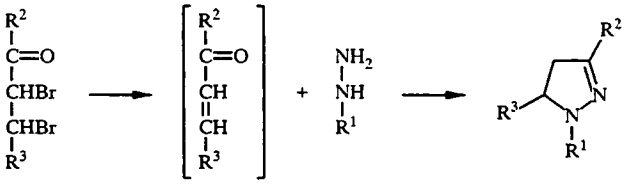


33 **41** **42**

Synthesis of 2-Pyrazolines by the Reaction of Chalcone Dibromides and Hydrazines

2-Pyrazolines **38** have also been prepared by the reaction of chalcone dibromides **43** with hydrazines (Scheme 17) [65-69]. The mechanism of the reaction has not been investigated, but it was supposed that the first reaction step is debromination providing chalcones [67] which then react with hydrazines to afford 2-pyrazolines as when chalcones are used as starting materials.

Scheme 17

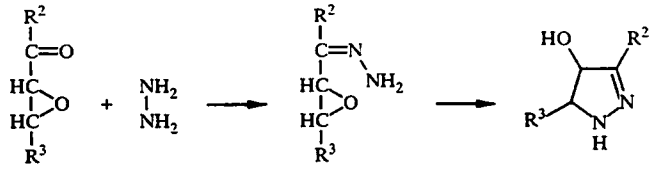


43 **33** **38**

Reaction of Chalcone Epoxides with Hydrazines

The reaction of chalcone epoxides and hydrazines has already been investigated in the early twentieth century [70-74]. However, owing to the conflicting data and the lack of unambiguous structure elucidation of the reaction products, it is difficult to judge whether hydrazone, pyrazole, or pyrazoline is actually formed. The first well-established experimental study on the reaction of chalcone epoxides **44** and hydrazine **45** was performed by Litkei et al. [75, 76] in 1972. On the basis of these experiments it has been concluded that hydrazone **46** is formed as a stable intermediate, the ring closure of which affords 3,5-diaryl-4-hydroxy-2-pyrazolines (**47**) (Scheme 18). The formation of 2-pyrazolines **47** by the reaction of chalcone epoxides and hydrazine was corroborated in the late eighties [77, 78].

Scheme 18

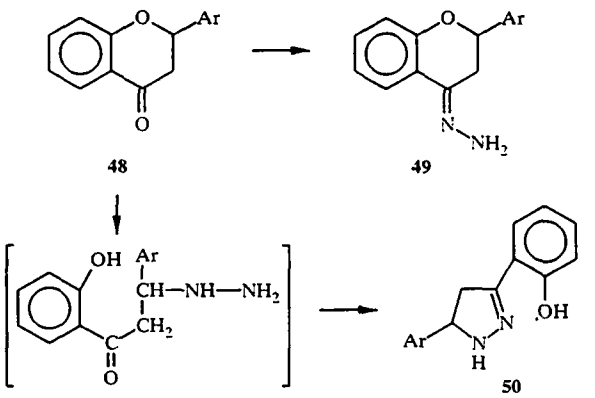


44 **45** **46** **47**

Preparation of 2-Pyrazolines by the Reaction of Flavanones with Hydrazines

A special procedure for the preparation of 2-pyrazolines is the reaction of flavanones with hydrazines [79-84]. This reaction has been thoroughly investigated by Kállay et al. [79, 82]. According to their assumption the formation of 2-pyrazoline **50** may proceed either via hydrazinolysis of flavanone molecule **48** or from the "favorable" stereoisomer of flavanone hydrazone **49** (Scheme 19).

Scheme 19

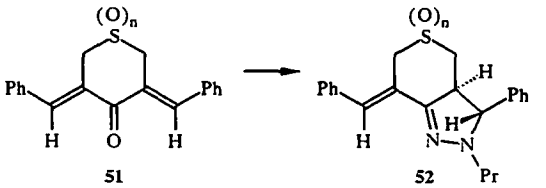


However, this procedure can be considered as one of the reactions of flavanones and not as an efficient method for the preparation of 2-pyrazolines since the same 2-pyrazolines are obtained from flavanones and 2-hydroxychalcones used as starting materials to synthesize the appropriate flavanones.

Synthesis of 2-Pyrazolines by the Reaction of Exocyclic α,β-Unsaturated Ketones with Hydrazines

Bicyclic tetrahydrothiopyrano [4,3-*c*]pyrazolines (**52**) have been synthesized by the reaction of tetrahydro-3,5-bis (phenylmethylene)-4H-thiopyran-4-one (**51**) and its S-oxides with *n*-propylhydrazine in hot methanol (Scheme 20) [85, 86]. A detailed NMR spectroscopic investigation of 2-pyrazolines **52** revealed a *trans* arrangement of protons at the chirality centers in the molecules (cf. Scheme 20).

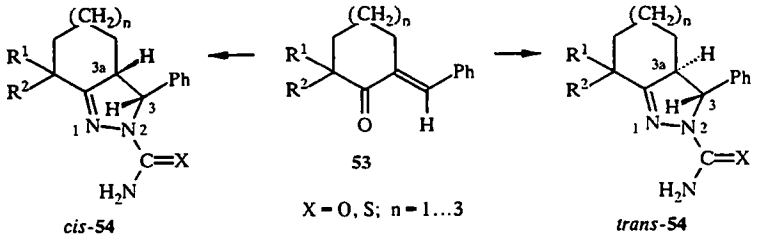
Scheme 20



n = 0, 1, 2

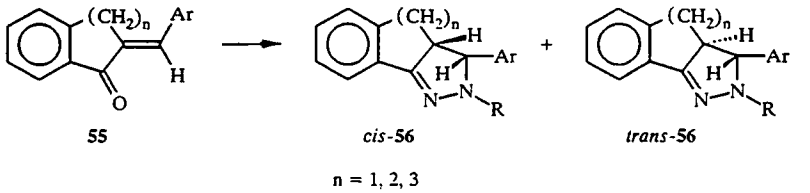
Loránd et al. [87] synthesized bicyclic 2-pyrazolines **54** by the reaction of benzylidenecycloalkanones **53** with semicarbazide or thiosemicarbazide in hot ethanol in the presence of hydrochloric acid (Scheme 21). Under such reaction conditions *cis/trans*-mixtures of bicyclic 2-pyrazolines are obtained which can be easily separated. The relative configuration and conformation of compounds **54** have been elucidated by NMR spectroscopy and X-ray crystallography.

Scheme 21



Tricyclic pyrazolines **56** have been synthesized by the reaction of 2-arylidene(benzocycloalkanones) **55** viz. 2-arylidene-1-indanones (**55**, n = 1), 2-arylidene-1-tetralones (**55**, n = 2), and 2-arylidene-1-benzosuberones (**55**, n = 3) with hydrazines under various reaction conditions (Scheme 22) [88-95].

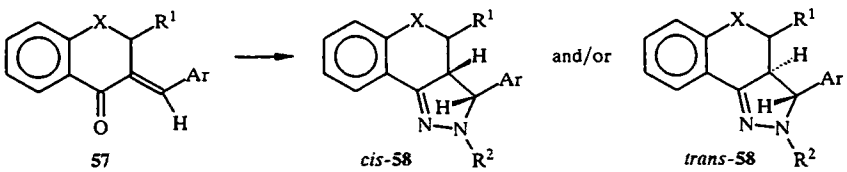
Scheme 22



In many cases, methanol or ethanol solutions of the appropriate α,β-enone **55** and hydrazine were refluxed for several hours, and the corresponding tricyclic pyrazolines **56** were obtained in good yields [88-92]. In some cases the two starting materials were allowed to react under acidic reaction conditions which provided generally the *cis/trans*-mixtures of such pyrazolines [87, 93]. The *cis/trans*-diastereomers can easily be separated and isomerize into each other [95]. However, when 2-benzylidene-1-tetralone (**55**, n = 2) and hydrazines were allowed to react in boiling pyridine the trans-isomers of the appropriate pyrazolines (*trans*-**56**) (cf. Scheme 22) were obtained in good yields [96, 97].

Stereoselective synthesis of [1]benzopyrano[4,3-*c*]pyrazolines (**58**, X = O) and [1]benzothiopyrano[4,3-*c*]pyrazolines (**58**, X = S) has been performed by the reaction of 3-arylidenechromanones (**57**, X = O) and their thio analogues (**57**, X = S) with hydrazines (Scheme 23) [96-100]. If α,β-enones **57** were allowed to react with hydrazines in hot pyridine solution, *trans*-**58** were obtained as sole products [96, 97]. Whereas *cis*-**58** were obtained as major products when the same reaction was performed in hot ethanol in the presence of hydrochloric acid (cf. Scheme 23), some *trans*-**58** as minor product could also be detected in the solution or was isolated and characterized.

Scheme 23



The literature data published up to the end of 1996 have been included to help the reader to find the original publication concerning an actual synthetic method.

The present project was sponsored by the Hungarian Ministry for Culture and Education, to which we express our gratitude.

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