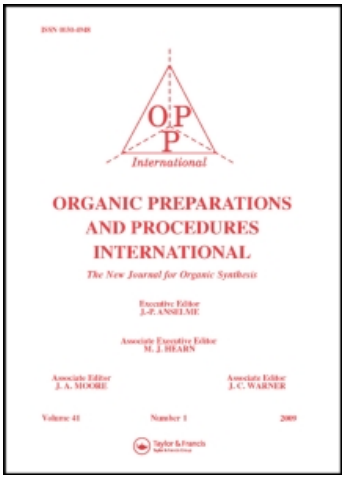

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RECENT ADVANCES IN THE REACTIONS OF HYDRAZINES AND HYDROXYLAMINES WITH (α,β-UNSATURATED AND β-DICARBONYL COMPOUNDS

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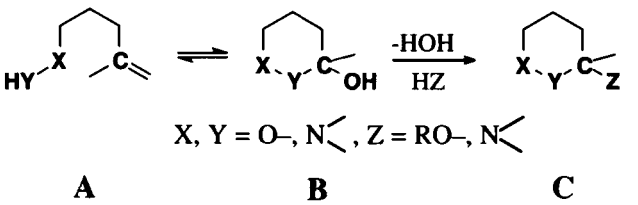
INTRODUCTION AND SCOPE

The interaction of hydrazines (hydroxylamines) with alkenals and alkenones, and with β-dicarbonyl compounds is known to be a method of synthesis of pyrazolines (isoxazolines) and pyrazoles (isoxazoles) respectively. Numerous 1,2-azoles and azolines have been prepared by this method. Their utility as synthons[1-4] and their chemistry have been discussed previously in reviews.[5-10] These substances, especially isoxazolines, are useful for the synthesis of 1,3-bifunctional reagents (e. g., various natural compounds and their analogs) because of the ready cleavage of the bond between heteroatoms.



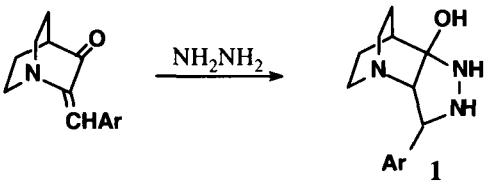
Scheme 1

These reactions may also be of interest from a different point of view: products of type **A** (***Scheme 1***) formed in the initial stage may be stable in the presence of certain structural factors. These products are monohydrazones or oximes preceding the corresponding azole formation in the reaction of β-dioxo compounds and β-hydrazino(hydroxylamino)carbonyl compounds resulting from Michael addition to alkenals and alkenones. The primary products are capable of ring-chain tautomerism. The cyclic forms **B** are hydroxypyrazolidines (isoxazolidines) or hydroxypyrazolines (isoxazolines) and may be considered as new azole representatives. The hemiaminal (hemiacetal) hydroxyl group in the latter substances can be replaced easily by alkoxy-, amino- and hydrazino groups. A number of new azoline (azolidine) derivatives **C** may be obtained by this approach. These problems have been

discussed earlier.[11] The present review reports detailed information on this matter, obtained during the last 35 years. Some other data regarding synthesis are also presented in this review. The literature has been surveyed to the end of 1994.

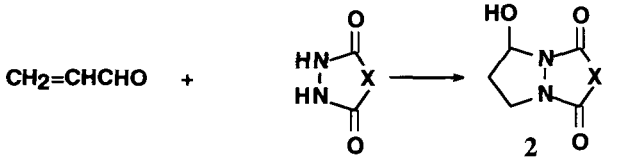
I. 5-HYDROXY-, ALKOXY-, AMINO- AND HYDRAZINOPYRAZOLIDINES

The intermediate formation of hydroxypyrazolidines in reactions of hydrazine and its mono-substituted derivatives with α,β-unsaturated aldehydes and ketones has been observed in few cases.[12,13] At the same time, hydroxytetrahydropyrazolo[4,3-*b*]quinuclidines **1** (***Eq. 1***) proved to be stable,[14] perhaps because of steric destabilization of their dehydration products.

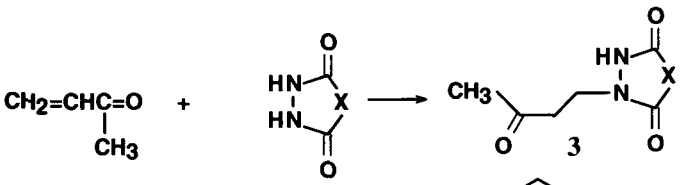


(1)

5-Hydroxypyrazolidines **2** are the main products of interaction between cyclic hydrazides and acrolein[15] (***Eq. 2***), while with methyl vinyl ketone, the products resulting from Michael addition have the linear structure **3** (***Eq. 3***).[15] Addition of cinnamaldehyde to phthalazine-1,4-dione with heating presumably leads to the corresponding condensed pyrazoline with indefinite position of the double bond.[16] These facts point out that the formation of pyrazolines from α,β-unsaturated carbonyl compounds and hydrazines could proceed through the addition of hydrazine to activated double bond of alkenal (alkenone) followed by ring closure and dehydration. Indeed, the formation of the corresponding Δ^2-pyrazoline from chalcone and phenylhydrazine *via* addition followed by favored 5-*endo-trig* cyclization has been demonstrated by ^{13}C and ^{15}N labelling in time resolved ^{13}C NMR spectroscopy.[17,18]

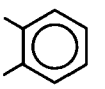


(2)



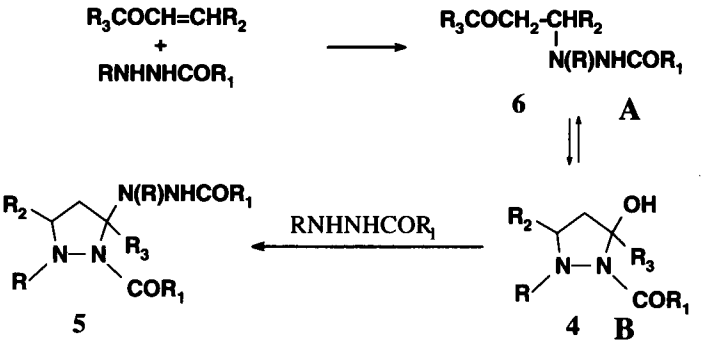
(3)

X = CEt_2, $-CH_2CH_2-$, -CH=CH-,



Similar results were observed for the interaction of alkenals[19,21] and methyl vinyl ketone with β-alkyl(aryl)hydrazides. With increasing reaction time and hydrazide concentration, however, instead

of 5-hydroxypyrazolidines **4,** 5-hydrazinopyrazolidines **5** are formed. They may be the main products of condensation in certain cases (***Eq. 4***) and can also be obtained from the reaction of hydrazides with 5-hydroxypyrazolidines **4**. The condensation of crotonaldehyde with hydrazobenzene gave the corresponding 5-hydrazinopyrazolidine as the sole product.[22] Products of the addition of hydrazides to methyl vinyl ketone are corresponding 4-hydrazinobutanones **6**,[20] while 5-hydroxypyrazolidines **4** are derived from alkenals.[19-21,23]

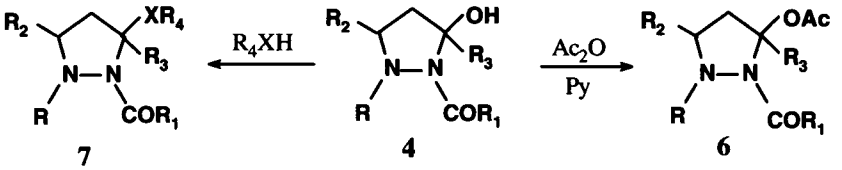


(4)

R = alkyl, aryl; R_1 = H, alkyl, aryl; R_2 = H, Me; R_3 = H, Me, Ph

However, ring-chain tautomerism **A-B** was observed for 5-hydroxypyrazolidines in polar solvents. In some cases, the cyclic tautomers predominate.[23] 5-Hydroxypyrazolidines substituted at the 3-position theoretically can form diastereomeric pairs. In fact however, only the *trans*-isomer with respect to the HO-group with the corresponding substituent in the 3-position is formed as was established by X-ray examination.[24] Therefore, addition of hydrazides to the double bond of alkenals is a stereoselective process.

The hydroxy group of 5-hydroxypyrazolidines **4** is sufficiently acidic[25] and active to be easily converted into 5-acyloxy-(**6**) and 5-alkoxydervatives **7** in reactions with anhydrides[11] and alcohols[26] respectively (***Eq. 5***). The same reaction takes place if thiophenol is added.[11] The hydroxy group can be replaced by the amino groups[26] as well as by hydrazine and hydroxylamine (compounds **8-10**, ***Eq. 6***).[27]

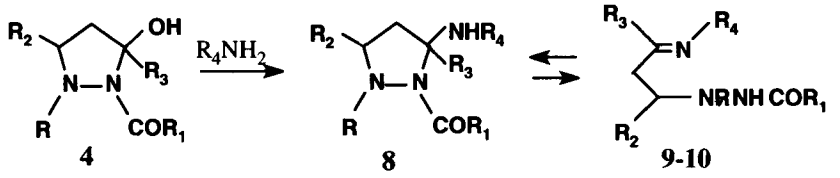


(5)

X = O, R_4 = alkyl; X = S, R_4 = Ph

It is noteworthy that the resulting products have different structures. 5-Amino-pyrazolidines **8** exist in the cyclic form in all solvents, while hydrazino- and hydroxyl-amino derivatives **9** and **10** have the open-chain form, though ring-chain tautomerism was observed in some solvents (DMSO-d_6,

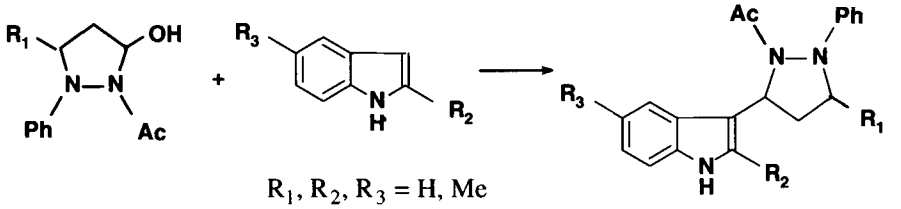
DMF-d_7). The structure of 5-hydroxy- and 5-aminopyrazolidines was investigated separately in the gas phase under electron impact.[28]



(6)

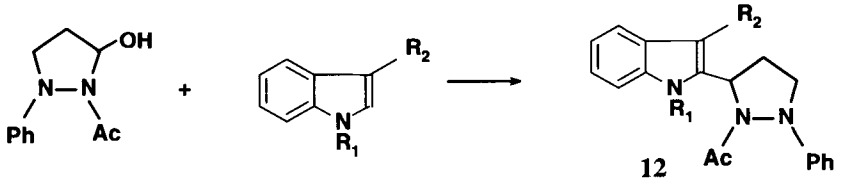
R_4 = aryl, NMe_2, p-$NO_2C_6H_4NH$, MeCONH, PhCONH, PhCSNH, OH

Substitution of the OH-group in reactions with C-nucleophiles is also possible as was demonstrated by the reaction of hydroxypyrazolidines with indoles (compounds **11** and **12**, ***Eq. 7*** and ***8***).[11]



(7)

R_1, R_2, R_3 = H, Me

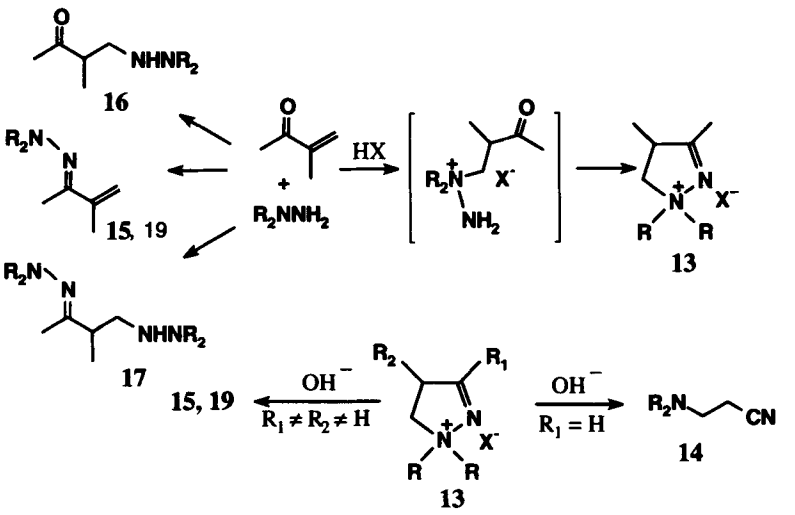


(8)

R_1 = H, Me; R_2 = Me, Ph

II. REACTION OF ALKENALS AND ALKENONES WITH 1,1-DIALKYLHYDRAZINES

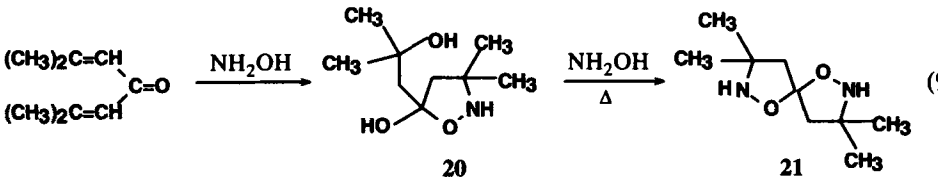
The reaction of 1,1-dialkylhydrazines with acrolein in the presence of equimolar amounts of acids begins with Michael addition of the substituted nitrogen atom, followed by cyclization to a 1,1-dialkyl-Δ^2-pyrazolinium salt **13** which may be isolated.[29] Alkaline decomposition of these salts **13** gives β-dialkylaminonitriles **14** (***Scheme 2***).[30-32] The use of other alkenals in this condensation leads to formation of unsaturated hydrazones **15** regardless of medium acidity.[36] They are sometimes accompanied by products resulting from addition to the double bond, *viz.*, N,N-dialkylhydrazinocarbonyl compounds **16** and β-hydrazinohydrazones **17**.[37] With α,β-unsaturated ketones,[33-35] the addition of alkali promotes Hofmann degradation of the pyrazolinium salts to form α,β-unsaturated hydrazones **19**.[34-35] Thus, acrolein dialkylhydrazones had been inaccessible until they were obtained by a special method of reagent injection into an alkaline solvent in order to avoid the aminonitrile rearrangement.[38]



Scheme 2

III. 3(5)-HYDROXY-, ALKOXY- AND AMINOISOXAZOLIDINES

There have been reports of the formation of stable primary products by addition of hydroxylamine to alkanals and alkenones.[39-42] Due to the relative stability of the primary product **20** in the reaction of hydroxylamine with phorone (***Eq. 9***) a bicyclic spiro compound **21** is formed.[42] On the other hand, 5-hydroxyisoxazolidines **22** are the main products of the reaction if N-alkyl- or arylhydroxylamines are used as substrates (***Eq. 10***).[43-46]



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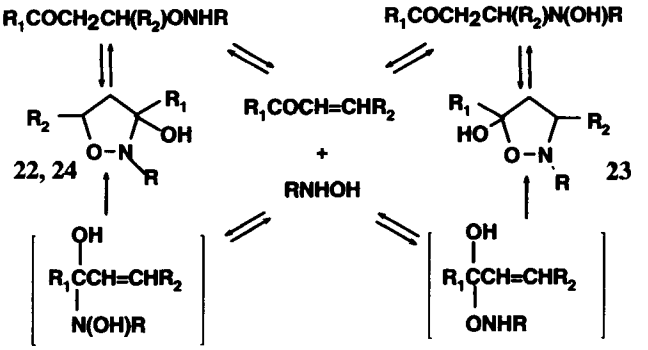


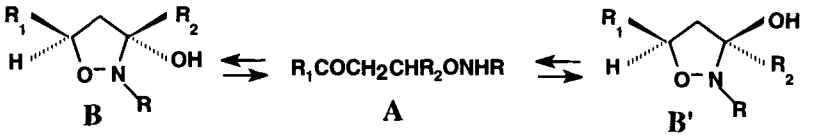
(10)

R = t-Bu, Ph, p-$NO_2C_6H_4$, $PhCH_2$, PhCO, p-MeC_6H_4CO, p-BrC_6H_4CO, p-$MeOC_6H_4CO$, p-$NO_2C_6H_4CO$, 2,4,5-$(Me)_3C_6H_2CO$, $CONH_2$; $R_1 = R_2 = H$, $R_1 = H$, $R_2 = Me$, $R_1 = Me$, $R_2 = H$

Depending on the reaction conditions and the substituents of the hydroxylamine, 3- and/or 5-hydroxyisoxazolidines (**23** and **24**) may be obtained through the same reaction with α,β-unsaturated carbonyl compounds.[46-50] Thus, benzohydroxamic acid and its *p*-nitro-, *p*-bromo- and 2,4,5-trimethyl analogs react with alkenals to produce 2-acyl-3-hydroxyisoxazolidines **23**, while the *p*-methyl- and *p*-methoxy derivatives form 5-hydroxyisoxazolidines **24**.[46] The exclusive products with hydroxyurea are 5-hydroxy derivatives **24**.[51]

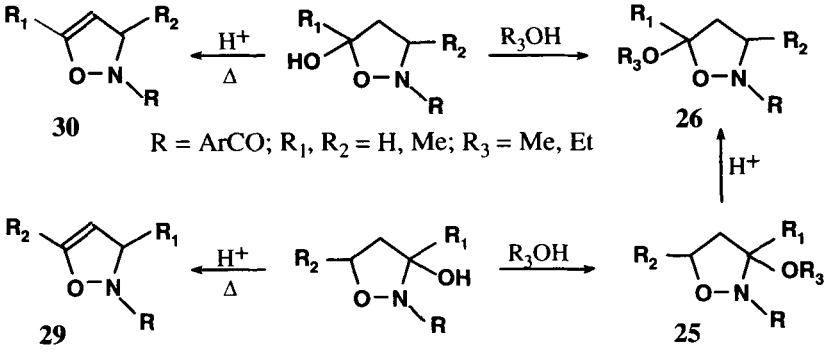
If the reaction is carried out on the surface of an adsorbent (alumina, silica gel, cellulose, etc.), both 3- and 5-substituted derivatives usually occur, the amount of each isomer being dependent on the nature of the nature of the solid adsorbent and the reaction time.[49-50] The process is reversible in its first stage. 3-Hydroxyisoxazolidines **23** and 5-hydroxyisomers **24** proved to be the kinetically and thermodynamically controlled products respectively. Thus, any particular isomer may be obtained by appropriate choice of the reaction time and solid adsorbent.

The ring-chain tautomerism **A-B** is typical for both 3- and 5-hydroxyisoxazolidines.[39,40,43,45,47,52] ***Eq. 11*** illustrates the equilibrium for 3-substituted derivatives. The proportion of tautomer **A** increases with increasing polarity of the solvent and predominates for methyl vinyl



(11)

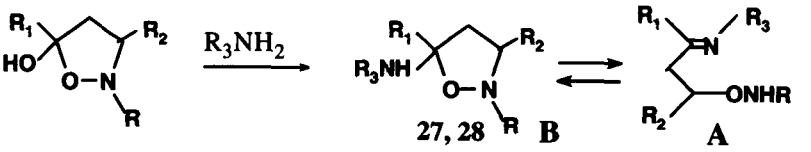
ketone derivatives. There is a greater tendency to form the cyclic structure **B** for 5-hydroxyisoxazolidines. The fact that the cyclic form is a mixture of comparable amounts of diastereomers **B-B'** in the case of crotonaldehyde derivatives shows that addition of N-substituted hydroxylamines to alkenals is a non-stereoselective process. The properties of the 3(5)-hydroxyisoxazolidines **23** and **24** are similar to those of the 5-hydroxypyrazolidines: the hydroxyl group possesses substantial acidity and activity and the reaction of the hydroxyisoxazolidines with alcohols leads to 3(5)-alkoxyisoxazolidines **25** and **26** (***Scheme 3***).[54]



Scheme 3

3(5)-Methyl-5(3)alkoxyisoxazolidines proved to be mixtures of diasteroisomers. Some of these mixtures have been separated and the isomer configuration determined.[56]

The reactions of hydroxyisoxazolidines with amines and hydrazines yield 3(5)-amino- and hydrazinoisoxazolidines **27** and **28**.[45-54] They display the ring-chain tautomerism **A-B** (***Eq. 12***).

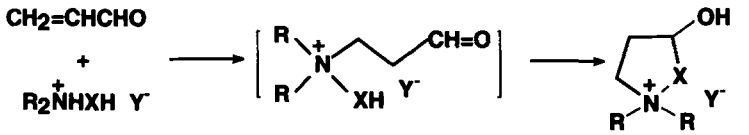


(12)

R = Ph, $PhCH_2$, ArCO; R_1, R_2 = H, Me; R_3 = $PhCH_2$, Ar, NMe_2

Alkoxy group exchange is also possible.[54] Recyclization of 3-alkoxyisoxazolidines **25** into 5-alkoxy derivatives **26** was reported in the presence of acids with increasing reaction time.[55] Aminoisoxazolidines **27** tend to exist in the cyclic form **B** while the linear form **A** predominates for hydrazino derivatives **28.** The dehydration to Δ^3- or Δ^4-isoxazolines **29, 30** is a common process for hydroxyisoxazolidines (***Scheme 3***).[39,57] Isoxazolines are of special interest in organic synthesis as compounds with activated double bonds and as precursors for the preparation of 1,3-aminoalcohols, C-acylazirines etc.[57]

Salts of N,N-dialkylhydroxylamines and N,N-dialkylhydrazides react with acrolein to give isoxazolidinium and pyrazolidinium salts **31** correspondingly (***Eq. 13***).[58]

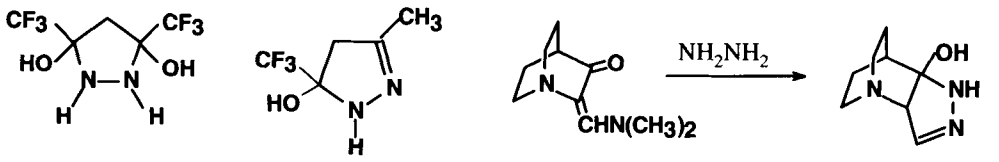


(13)

X = O, NAc, Y = Cl, CF_3CO_2 **31**

IV. 5-HYDROXY- AND 5-HYDRAZINO-Δ^2-PYRAZOLINES

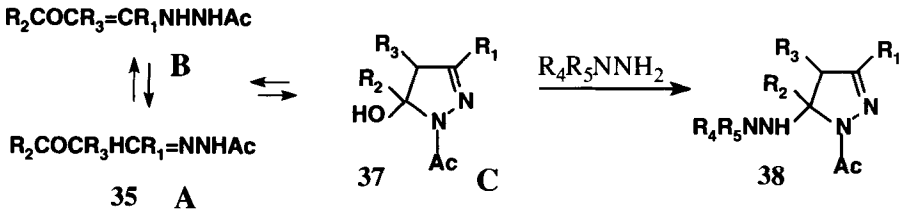
All possible intermediates resulting from interactions of 1,3-dicarbonyl compounds with hydrazine and its alkyl- and aryl derivatives have been detected by special NMR techniques.[59-63] In spite of this fact only in a few cases can stable products be isolated. In one particular case, the corresponding dihydroxypyrazolidine **32**, stabilized by the electron-withdrawing effect of the two trifluoromethyl groups, could be isolated in the reaction of hexafluoroacetylacetone with hydrazine (***Scheme 4***).[64,65] The corresponding 5-hydroxy-Δ^2-pyrazoline **33**, stabilized by the electron-withdrawing effect of the one trifluoromethyl group, could be obtained by the condensation of hydrazine with trifluoroacetylacetone[65] as its analogs could be synthesized from hydrazine and other 1,3-diketones with perfluoroalkylated groups.[66] Surprisingly, dihydropyrazolo-[4,3-*b*]quinuclidine with 5-hydroxy-Δ^2-structure **34** proved to be stable (***Scheme 4***).[67]



32 33 34

Scheme 4

If hydrazides are used, then corresponding monohydrazones **35** are usually stable due to the electron-withdrawing effect of the acyl group. These compounds demonstrate a three component equilibrium **A-B-C** (***Scheme 5***).[68-75,76,77,81-82] The predominant product in that equilibrium depends on the dicarbonyl compound used.

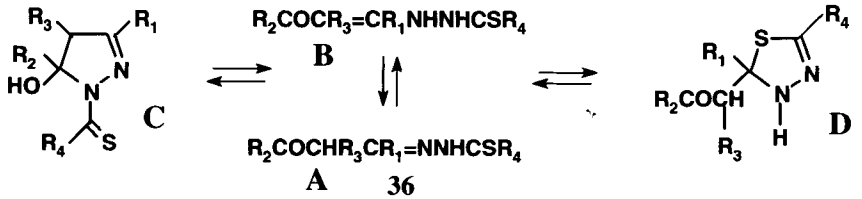


R_1 - R_2 = H, alkyl, aryl, R_3 = H, alkyl

R_4, R_5 = alkyl, H and COAlk, COAr, CONHR, CSN< , $CR=NH_2^+X^-$

Scheme 5

It should be noted that monohydrazones **36** derived from 1,3-dicarbonyl compounds and thioacylhydrazines display the ring-ring tautomerism **A-B-C-D** (***Eq. 14***).[78-80] As a result of these factors, modification of various mixtures containing up to four forms can be designed.



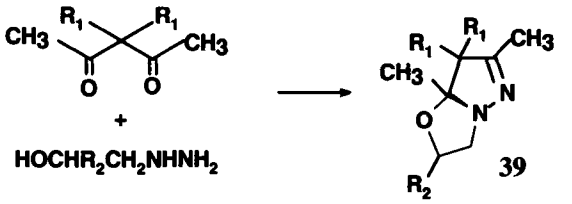
(14)

R_1 - R_2 = H, alkyl, aryl; R_3 = H, alkyl; R_4 = aryl, $PhCH_2$

5-Hydroxy-Δ^2-pyrazolines **37** react with hydrazides and N,N-dimethylhydrazine to afford the corresponding 5-hydrazino-Δ^2-pyrazolines **38** (***Scheme 5***).[83-86] Although these compounds are isomeric to 1,3-*bis*-hydrazones, no isomerization was observed. Moreover, compounds known as 1,3-*bis*-thiosemicarbazones also proved to have the structure of hydrazinopyrazolines.[72]

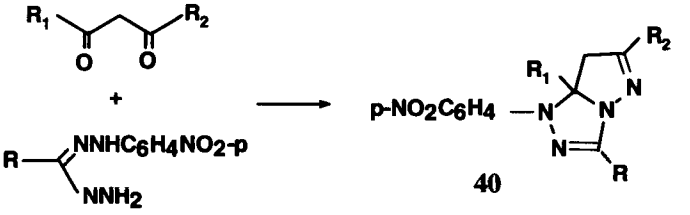
The ability of the hydroxyl group to be substituted with nucleophiles was used for the synthesis of condensed derivatives of pyrazole. If the hydrazine molecule contains an additional nucleophilic group, a number of previously unknown cyclic structures may be isolated. Derivatives of 3,3*a*,5,6-

tetrahydropyrazolo[3,2-*b*]oxazole **39** (***Eq. 15***)[87] as well as their nitrogen analogs **40** (**Eq. 16**)[88] were obtained in such a way.



(15)

R_1 = Me, HC≡CCH$_2$; R_2 = H, Ph, CH$_2$N(CH$_2$CH$_2$)$_2$NMe

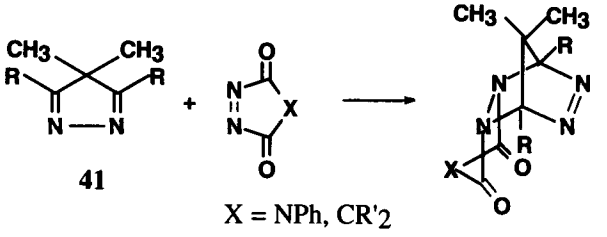


(16)

R = t-Bu, Ar; R_1 = Me, Ph; R_2 = H, Me

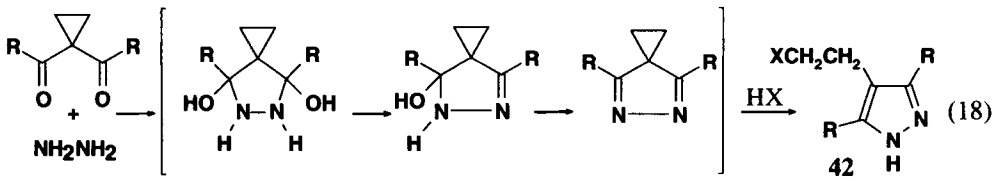
V. 4H-PYRAZOLES AND 5-METHYLENE-Δ²-PYRAZOLINES

The use of α,α-disubstituted 1,3-dicarbonyl compounds is another way to prevent 1H-pyrazole formation with hydrazine derivatives. With hydrazine itself, the reaction leads to the 4H-pyrazoles **41**.[89] These substances possess a number of valuable properties, especially in 1,4-cycloaddition (***Eq. 17***).[90-94]



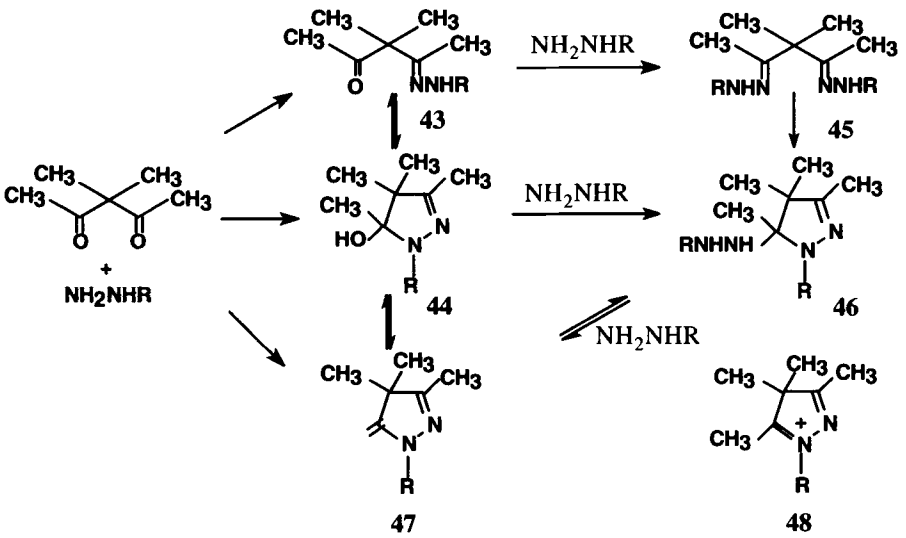
(17)

The condensation of hydrazine with 1,1-diacylcyclopropanes present interesting possibilities from the point of view of organic synthesis if the reaction is carried out in the presence of various reagents of the general formula HX. This reaction was shown to be a means for the synthesis of pyrazoles **42** containing β-functional substituents X in the 4 position. The individual steps were investigated by NMR spectroscopy (***Eq. 18***).[95-98]



R = Me, cyclopropyl, Ph, b-Py; X = Cl, Br, I, OMe, OEt, MeOCO, CN, NEt_2

The reactions of monosubstituted hydrazines (alkyl-, arylhydrazines and hydrazides) with α,α-dimethylacetylacetone can give varying results (***Scheme 6***).[99-100] Under mild conditions, monohydrazones **43** are formed when the ratio of reagents is 1:1; they undergo isomerization to corresponding 5-hydroxy-Δ^2-pyrazolines **44** in the presence of acid catalysts on heating. When excess hydrazine is added, the monohydrazones are converted into *bis*-hydrazones **45** while 5-hydroxypyrazolines give 5-hydrazino-Δ^2-pyrazolines **46** that can also be obtained from the *bis*-hydrazones as a result of thermal



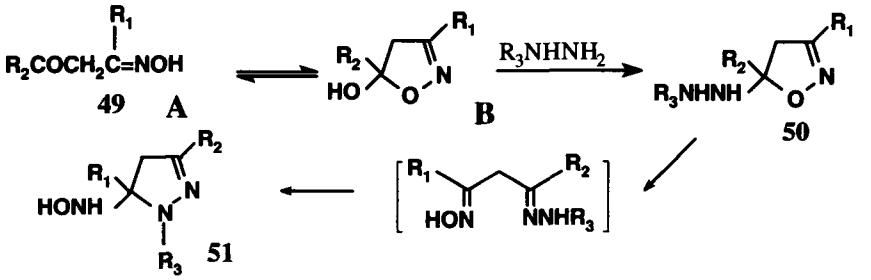
R = Me, Et, $PhCH_2$, i-Pr, Ph, 2,4-$(NO_2)_2C_6H_3$, MeCO, PhCO

Scheme 6

cyclization. Under more severe conditions, all these compounds give 5-methylene-Δ^2-pyrazolines **47** which are converted back to 5-hydroxy- or 5-hydrazino derivatives if water or a monosubstituted hydrazine is added. The above mentioned substances form 1-substituted 3,4,4,5-trimethylpyrazolium salts **48** in the presence of acids. Among these compounds 5-methylene-Δ^2-pyrazolines **47** are of value from the point of view of synthesis. Their oxidation to pyrazolones and other derivatives of pyrazole[101] as well as the cycloaddition of nitrile oxides[102] and nitrilimines[103] to their double bond were thoroughly investigated.

VI. REACTIONS OF 1,3-DICARBONYL COMPOUNDS WITH HYDROXYLAMINES

Readily available monooximes of β-dicarbonyl compounds **49** exhibit chain-ring tautomerism **A-B** (***Scheme 7***).[104-108] The hydroxy group in the cyclic tautomers, 5-hydroxy-Δ^2-isoxazolines **B**, is readily replaced by hydrazines (hydrazides) to give 5-hydrazino-Δ^2-isoxazolines **50**.[109,110] These

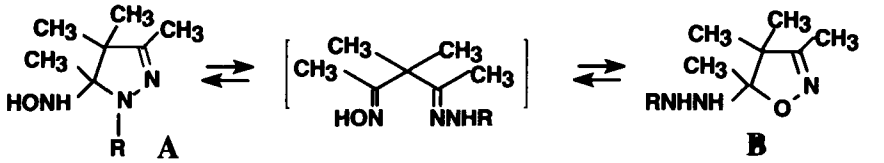


R_1 - R_2 = H, alkyl, aryl; R_3 = alkyl, H and COAr

Scheme 7

compounds which may be regarded as oximino hydrazones of β-dicarbonyl compounds, are tautomeric to 5-hydroxylamino-Δ^2-pyrazolines **51**. However, the formation of the open-chain compounds was not observed. 5-Hydroxylaminopyrazolines are formed if R_1 = H. In other cases these derivatives have the structure of 5-hydrazino-Δ^2-isoxazolines **50**.

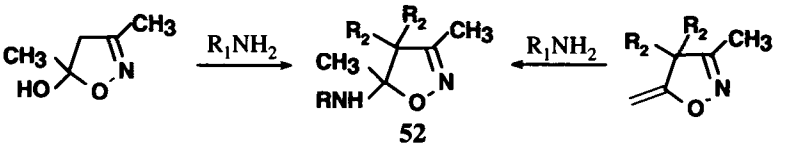
The ring-ring tautomerism **A-B** was observed for some "β-hydrazonooximes" of α,α-dimethylacetyacetone (***Eq. 19***).[111]



(19)

R = Me, Et, i-Pr, $PhCH_2$, Ph, MeCO, PhCO

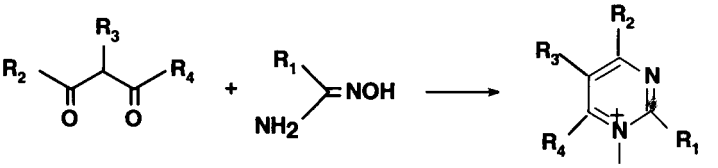
5-Amino-Δ^2-isoxazolines **52** have been obtained by reaction of amines with 5-hydroxy-isoxazolines and with 5-methylene-Δ^2-isoxazoline resulting from interaction of α,α-dimethylacetylacetone with hydroxylamine (***Eq. 20***).[112]



(20)

R_1 = H, alkyl, aryl; R_2 = H, Me

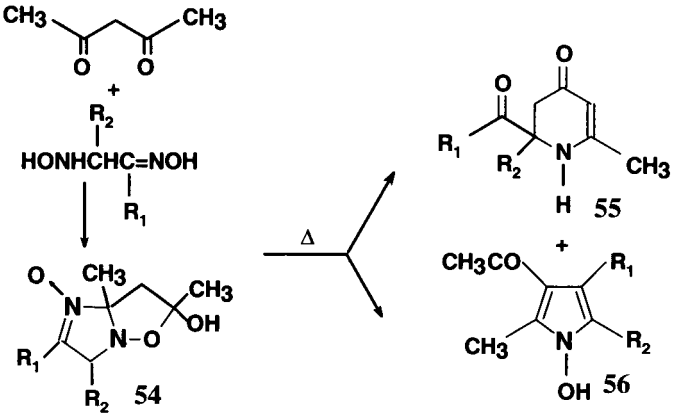
The interaction of 1,3-dicarbonyl compounds with such derivatives of hydroxylamine as amidoximes is a convenient method for the synthesis of pyrimidine N-oxides **53** (***Eq. 21***).[113]



(21)

R_1 = Me, Ar, Py, R_2 - R_4 = H, Me **53**

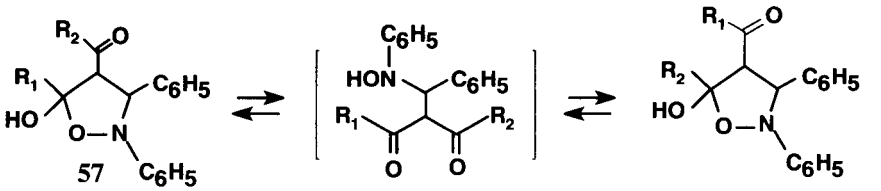
Addition of α-hydroxylaminooximes to acetylacetone leads to tetrahydroimidazo[1,2-*b*]isoxazole derivatives **54** which give 4-oxotetrahydropyridines **55** and 1-hydroxypyrroles **56** on thermolysis (***Eq. 22***).[114]



(22)

R_1 = Me, Ph; R_2 = Me, R_1 - R_2 = $(CH_2)_3$, $(CH_2)_4$, $(CH_2)_5$

Ring-ring tautomerism **A-B** is typical for 4-acyl-5-hydroxyisoxazolidines **57** resulting from interaction of 1,3-dicarbonyl compounds with nitrones (***Eq. 23***).[115]



(23)

A R_1 - R_2 = Me, CD_3, Et, Ph **B**

VII. CONCLUSION

The routine application of the reaction of alkenals and alkenones and β-dicarbonyl compounds with hydrazines and hydroxylamines has not been discussed in this review since data concerning 1,2-azolines (azoles) that can be obtained by these reactions are of interest mainly for chemists dealing with heterocycles or for pharmacologists investigating physiologically active compounds of these groups. The data reported here deal with novel synthetic application of the above mentioned reactions.

The main advantage of the synthetic methods herein described is an opportunity to obtain isoxazolidine (pyrazolidine) or isoxazoline (pyrazoline) derivatives containing hydroxy-, alkoxy-, amino- or hydrazino groups. The synthesis of 1,3-bifunctional synthons *via* 1,2-azolines (azolidines) had previously been possible only from the 1,3-cycloaddition of nitrones, nitrile oxides or nitrilimines. 1,2-Azolines (azolidines) substituted with above mentioned substituent groups had not been available by these latter routes, except for the alkoxy derivatives. Thus the 1,2-azoline (azolidine) method broadens significantly the synthesis of 1,3-bifunctional synthons. The aminonitrile decomposition of 1,1-dialkyl-Δ^2-pyrazolinium salts leading to β-dialkylaminonitriles may be regarded as an example.[29-31] Another example is the use of 5-amino-Δ^2-isoxazolines to obtain 1,3-amino-alcohols and β-aminooximes.[116]

Some products of linear structure (especially α,β-unsaturated hydrazones) are also useful as diene components of 1,4-cycloaddition in the synthesis of various pyridine derivatives.[117-118] The use of hydrazines and hydroxylamines with additional reactive groups (β-hydroxyalkylhydrazines, hydrazidines, α-hydroxylaminooximes) in condensations with 1,3-dicarbonyl compounds should also be noted since it is a convenient way for synthesizing new condensed heterocycles containing the 1,2-azole fragment.

1-Acyl(thioacyl)-5-hydroxy-Δ^2-pyrazolines are of interest as polydentate ligands since their linear hydrazone tautomers form complexes with metal cations.[119-123] Some of the nickel and copper chelates of thioacylhydrazones of β-diketones display antimicrobial activity.[124-125] It is noteworthy that some 5-hydroxy- and 5-hydrazinopyrazolidines show anti-inflammatory effects.[21] The hydrazinopyrazolines which result from the reaction of acetylacetone with thiosemicarbazide and from its N^4-alkyl homologs show antitumor activity.[126,127] It should be noted that these thiosemicarbazide derivatives were considered earlier as β-*bis*-hydrazones.[128] Analogously, certain corrections concerning the structure of β-*bis*-acylhydrazones have been made.[129] As already mentioned, they also have the 5-hydrazinopyrazoline structure.

The study of the reactions discussed is of theoretical interest. The ring-ring tautomeric equilibria with participation of various derivatives of nitrogen heterocycles have been discovered for the first time and special attention has been paid to this phenomenon.[130] Thus, it is hoped that the progress in this area will promote further fruitful research.

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