FURTHER DEVELOPMENT OF THE KETOXIME-BASED PYRROLE SYNTHESIS

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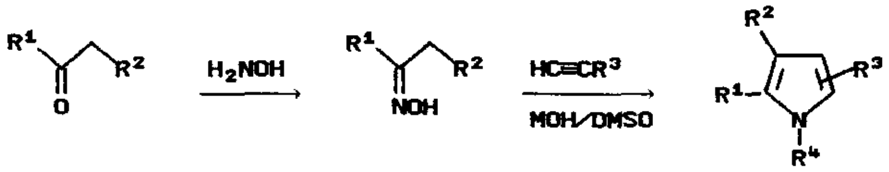
Dedicated to Professor Alan R.Katritzky on the occasion of his 65th birthday

Abstract - Recent development and modification of the general synthesis of pyrroles and 1-vinylpyrroles by the reaction of ketoximes with acetylenes and their synthetic equivalents (vinyl halides and dihaloalkanes) in the presence of the strongly basic KOH/DMSO catalytic and eliminating pair (the Trofimov reaction) are briefly reviewed. The formation of 3*H*-pyrroles and other isolable intermediates (*O*-vinyl ketoximes and hydroxypyrrolines) as well as side products are discussed.

1. Introduction

During the last two decades a general versatile method for the preparation of pyrroles from ketoximes and acetylenes or their synthetic equivalents (the Trofimov reaction[1]) amenable to large-scale synthesis keeps being steadily developed. This method has allowed the two-step transformation of ketones into pyrroles and their *N*-vinyl derivatives to be realized. In principle, the synthesis can be brought about as a one-pot procedure by treating ketones with hydroxylamine and then reacting the ketoximes formed with acetylenes (Scheme 1).



R^1, R^2 = alkyl, alkenyl, aryl, heteroaryl

R^3 = H, Me, Ph

R^4 = H, CH_2=CH, PhCH=CH

M = Li, Na, K, Rb, Cs

Scheme 1

This reaction has given a new push to the pyrrole chemistry and physicochemistry and, for a comparatively short time, scores of papers, patents, and theses have mushroomed in this area, which have been summarized in the reviews[2-11] and monographs.[12-16] Nevertheless, we are still far from having exhausted the possibilities the reaction offers.

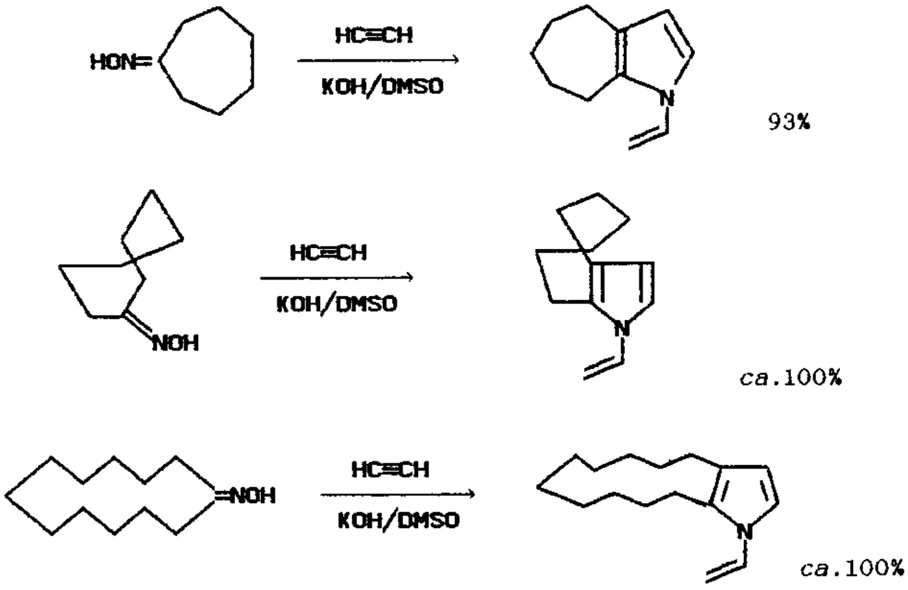
Here we analyze critically the most recent publications, mainly of the last five years, related to the ketoxime-based pyrrole synthesis which were not yet reviewed elsewhere with emphasis on developing procedures of preparative value.

2. Synthesis of Pyrroles from Ketoximes and Acetylenes and Their Synthetic Equivalents

For a few last years, reports on the pyrrole synthesis from ketoximes and acetylenes continue to appear. These include oximes of cyclic, heterocyclic, unsaturated, aromatic and heteroaromatic ketones, thus again confirming facile access to many otherwise difficultly obtainable pyrroles. Also, attention was paid to the utilization of vinyl halides and dihaloalkanes, instead of acetylenes, in this reaction, as well as to the isolation of intermediates and side products.

2.1. From Cyclic and Heterocyclic Ketoximes

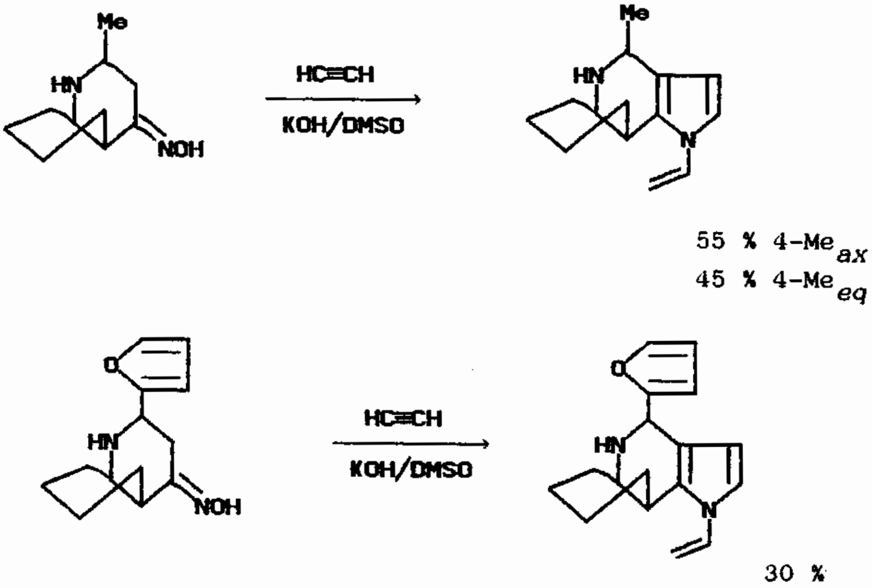
Oximes of cyclic ketones react readily with acetylene in the KOH/DMSO system to afford pyrroles and/or their *N*-vinyl derivatives in high yields (Scheme 2). The original paper[17] with more examples has been thoroughly covered in the recent review[11] and monograph.[16]



Scheme 2

The formation of pyrrolo[3,2-*c*]piperidines and pyrrolo[3,2-*c*]decahydroquinolines from oximes of 1,2,5-trimethyl-4-piperidone, 2-methyl- and 2-(2-furyl)-4-oxodecahydroquinolines upon treatment with acetylene (Scheme 3) and stereochemistry of the reaction have been recently studied[18] and some results being already briefly included in.[11,16]

Oximes of 2,5-dimethyl- and 1,2,5-trimethyl-4-piperidones (**1**) give also 1,2,3,4-tetrahydropyrrolo[1,2-*c*]pyrimidines (**3**) in a yield up to 20% due to the alternative participation of the CH-moiety adjacent to the oxime function followed by rearrangement and aromatization of the intermediate 3*H*-pyrroles **2** (Scheme 4).[8,18-25]

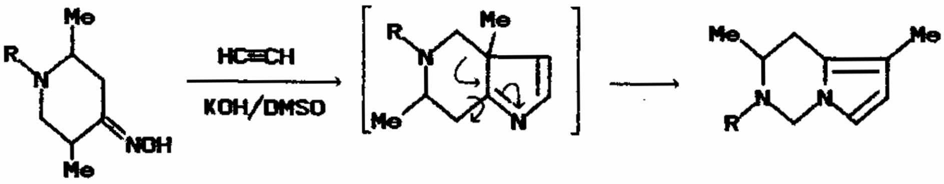


55 % 4-Me$_{ax}$
45 % 4-Me$_{eq}$

30 %

Scheme 3

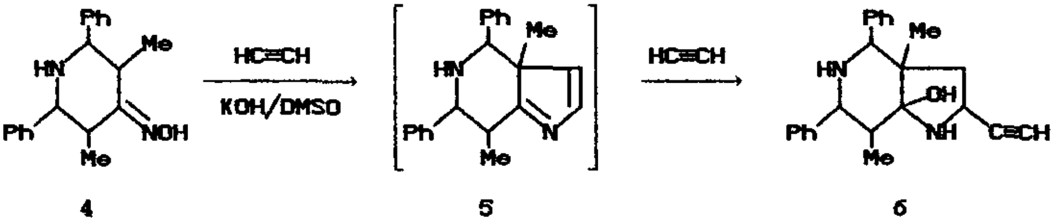
However, oxime of 3,5-dimethyl-2,6-diphenyl-4-piperidone (**4**) reacts with acetylene under pressure (80-90^{o}C, 15 atm) to afford four isomeric ethynyl perhydropyrrolo[3,2-*c*]pyridine (**6**) in a total yield of ~10% (Scheme 5).[21,22,24]



1 **2** **3**

R = H, Me

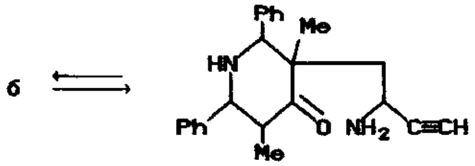
Scheme 4



Scheme 5

According to the ^{13}C (100.6 MHz) and two-dimensional ^{1}H nmr (400 MHz) data, isomers of **6** differ both by annelation mode and spatial orientation of the ethynyl group (*cis* or *trans* relative to 3a-Me).

The isomer pair (**6**) with axial equatorial annelation has been found (by two-dimensional NOESY spectra) to exist in equilibrium with the keto tautomers (**7**) (*Scheme* 6).[21,24]



7

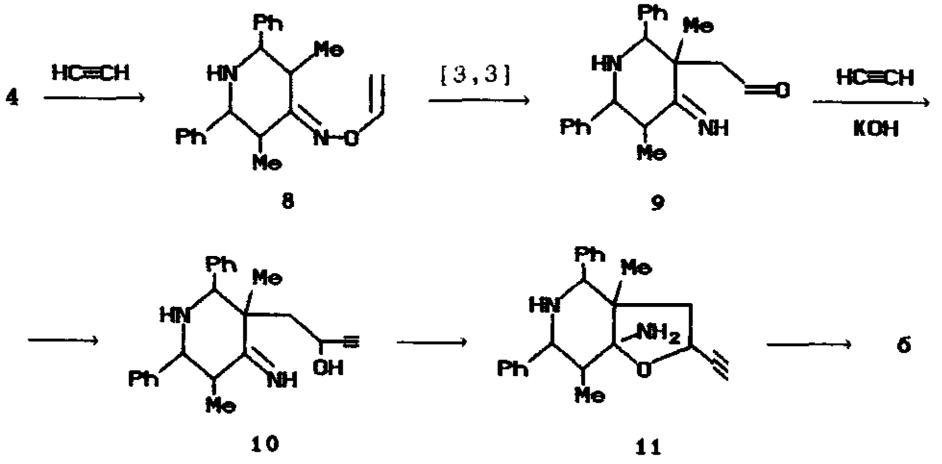
Scheme 6

The formation of **6** has been rationalized[22,24] in terms of the addition of molecules of water and acetylene to the intermediate 3*H*-pyrrole (**5**). However, since no example of the Markovnikov addition of acetylene to the C=C bond of enamines seems to be known, the alternative pathway leading to **6** might be also considered (Scheme 7).

The key step of Scheme 7 is the interception of the aldehyde (**9**) by acetylene (Favorsky reaction) to arrive at the acetylenic alcohol (**10**), which then cyclizes into **11** and the latter rearranges into **6**.

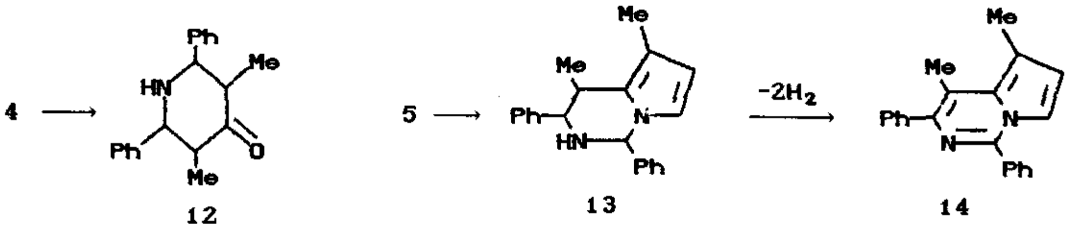
When the reaction was carried out under atmospheric pressure, 3,5-dimethyl-2,6-diphenyl-4-piperidone (**12**) and 4,5-dimethyl-1,3-diphenylpyrrolo[1,2-*c*]-

pyrimidine (**14**) have been isolated in small yields (Scheme 8)[24], the latter being resulted from dehydrogenation of the expected tetrahydropyrrolopyrimidine (**13**).

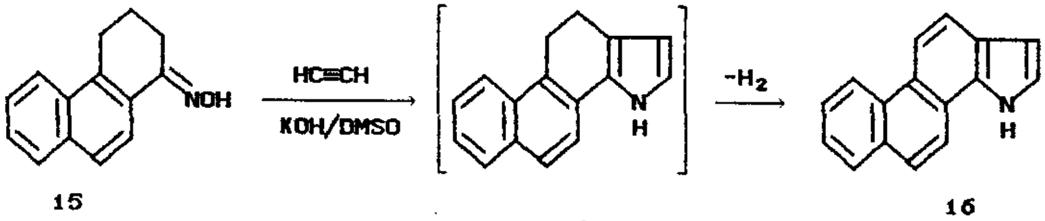


Scheme 7

The dehydrogenation has been observed in the synthesis of naphtho[1,2-*g*]indole (**16**) (55% yield) from oxime of 1-keto-1,2,3,4-tetrahydrophenanthrene (**15**) (Scheme 9) and acetylene under atmospheric pressure (KOH/DMSO, heating at 60-70°C up to a complete reacting of the starting oxime and then at 130-140°C for 8 h).[26,27]

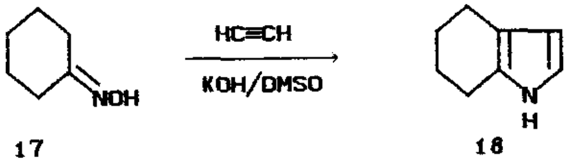


Scheme 8



Scheme 9

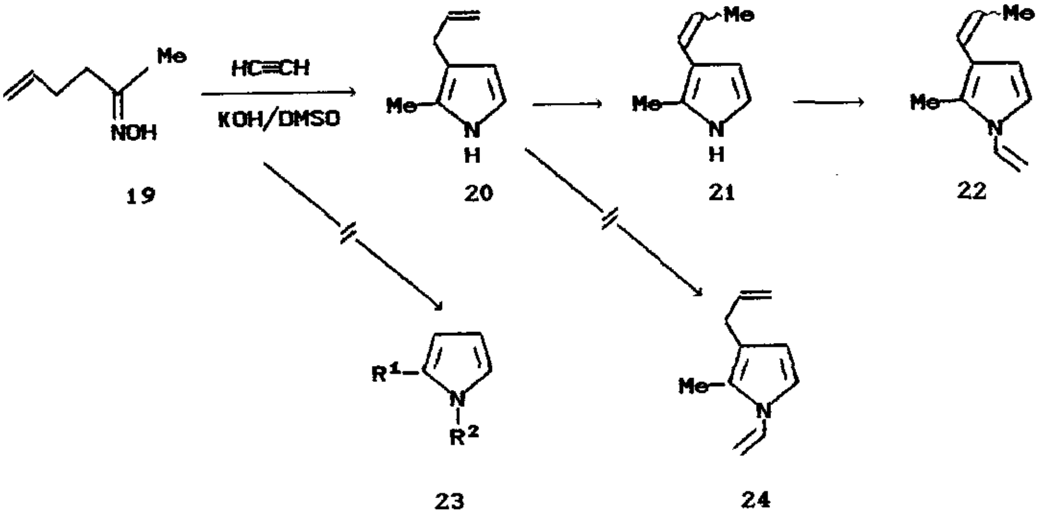
The synthesis of 4,5,6,7-tetrahydroindole (**18**) from cyclohexanone oxime (**17**) and acetylene[2-12,14-17] under atmospheric pressure (75-85°C has recently been improved to increase the yield up to 93% at a 95% conversion of **17** (Scheme 10).[28]



Scheme 10

2.2. From Alkenyl Ketoximes

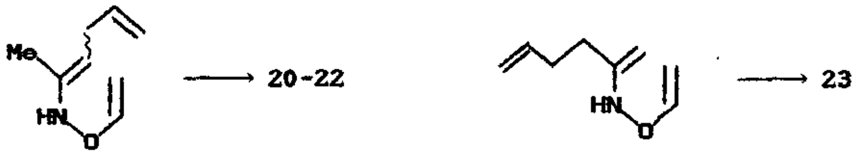
The reaction of alkenone oximes with acetylene in the KOH/DMSO system was proved to be a convenient route to 3-alkenylpyrroles.[29] Recently, more detailed data on the pyrrolization of 5-hexene-2-one oxime (**19**) have been published.[30] The unsaturated substituent of the starting oxime allows the reaction scope to be extended due to the controlled prototropic shift of the double bond (Scheme 11).



R^1 = butenyl; R^2 = H, CH_2=CH

Scheme 11

The isomerization **20** ⟶ **21** proceeds up to a 93% content of **21** with the E:Z ratio being 7:3. Within the 90-110°C temperature range the reaction remains regiospecific to give no pyrroles (**23**) constructed with the participation of the methyl group. It implies the reaction to follow *via* the key intermediate (**25**) rather than **26** (for a detailed reaction mechanism see in[11,16]), the former being expected thermodynamically more preferable (Scheme 12).



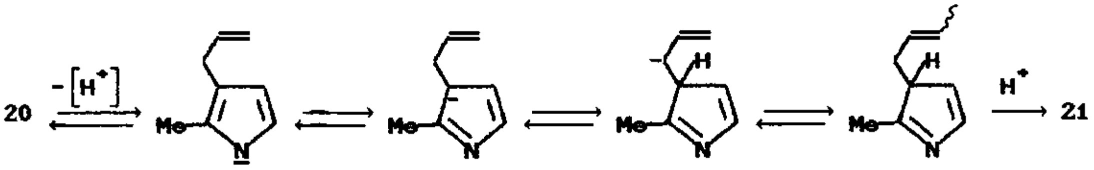
25 **26**

Scheme 12

The non-isomerized pyrrole (**20**) can be isolated in 80% yield (based on the oxime consumed) from the reaction carried out at atmospheric pressure (90-95°C, 2.5 h). The isomerized pyrrole (**21**) can also be prepared directly from the oxime (**19**). However, it is much more convenient to separately isomerize the pyrrole (**20**) with the KOH/DMSO suspension under anhydrous conditions at 110°C, the system reaching the equilibrium state for 1.5 h (ΔH = 58 kJ·mol^{-1}, in favor of **21**).[30]

The 1-vinylpyrrole (**22**) was obtained in 80% yield in an autoclave (10 atm, 110°C, 3 h) with excess acetylene.

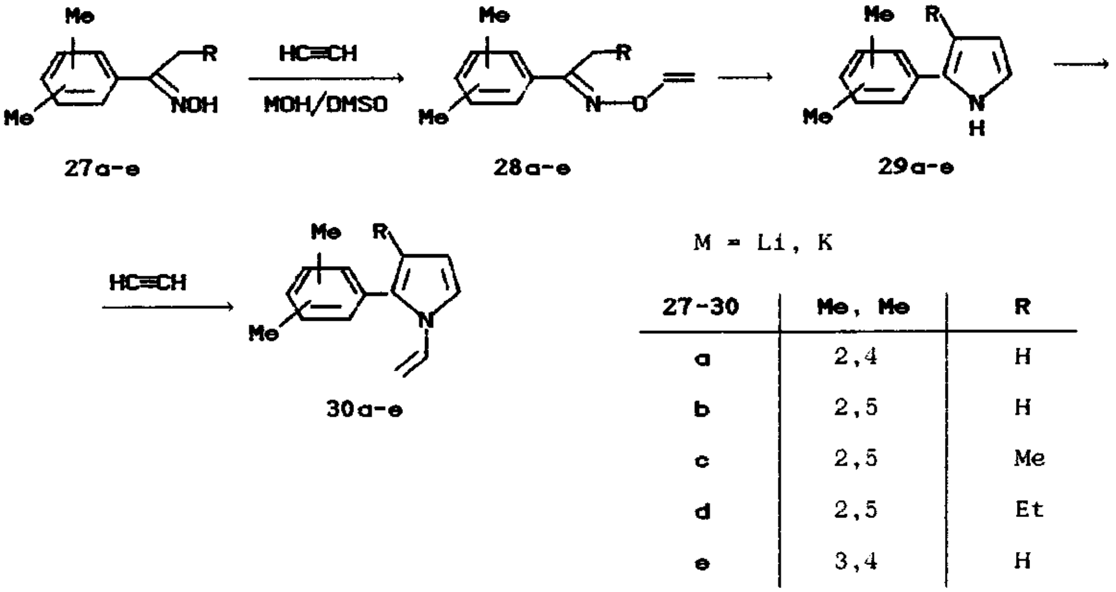
1-Vinylpyrrole (**24**) was not detected in the reaction mixture to imply that the facile ionization of the pyrrole (**20**) prior to vinylation contributes to a prototropic shift of the substituent double bond *via* the transfer of the anionic center from nitrogen into the substituent (Scheme 13).



Scheme 13

2.3. From Aryl and Heteroaryl Ketoximes

2-(2,4-, 2,5- and 3,4-Dimethylphenyl)pyrroles (**29**), (**30**) have been synthesized from the corresponding oximes (**27**) (Table 1) for the further study of the conjugation of the pyrrole nucleus with unsaturated and aromatic structural units as dependent on coplanarity (Scheme 14).[14,31]



M = Li, K

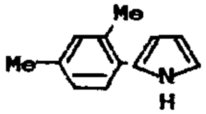
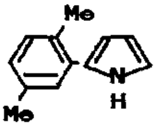
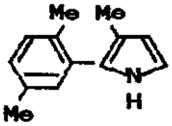
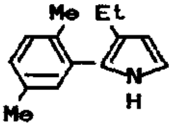
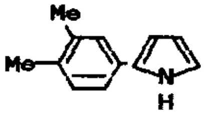
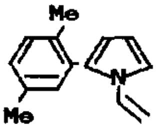
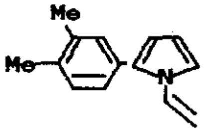
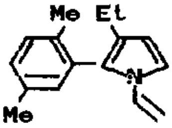
27-30	Me, Me	R
a	2,4	H
b	2,5	H
c	2,5	Me
d	2,5	Et
e	3,4	H

Scheme 14

In some runs, a partial deoximation to release the corresponding acetophenones has been observed.[31]

To better outline the scope and limitations of the Trofimov reaction, new families of aryl ketoximes are being attempted to be involved into pyrroliz-

Table 1. Synthesis of 2-Dimethylphenylpyrroles (KOH, 12 atm C_2H_2)[31]

Pyrrole		Reaction temp. (°C)	Reaction time (h)	Yield (%)
29a		130	3.5	49(6)[a]
29b		130	3.5	49(6)[a]
29c		70	6.0	39[b]
29d		70	6.5	45[b]
29e		130	3.5	48(7)[a]
30b		100	3.0	51
30e		100	3.0	52
30d		115	3.0	52

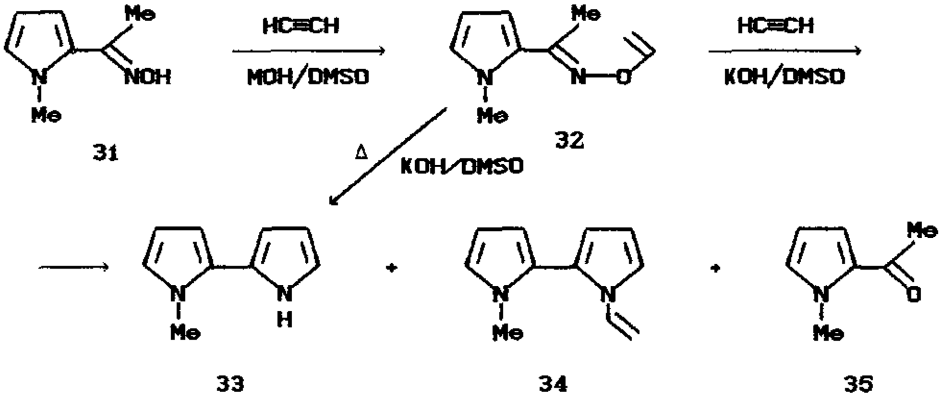
[a] In the brackets, the yields of the correspoing 1-vinylpyrrole of the same run are given.

[b] In the reaction mixture, the corresponding *O*-vinyl ketoxime also was detected.

ation with acetylene (Tables 2,3).[32,33] 1-Vinyl-2-(4-vinyloxyphenyl)pyrrole (Table 3) was prepared both from 4-bromophenyl methyl ketoxime and 4-hydroxyphenyl methyl ketoxime.[33] The low (non-optimized) yield (11%) of 2-(4-fluorophenyl)pyrrole is mainly due to a more pronounced deoximation (particularly with calcined KOH in dry DMSO) of the starting ketoxime to 4-fluoroacetophenone (up to 24%) as compared with other aryl ketoximes, and also due to the expected saponification of the fluorine atom.

The attempted pyrrolization of perfluorophenyl methyl and 4-nitrophenyl methyl ketoximes failed[23], the latter being recovered from the reaction mixture[33,36] and 2-phenylpyrrole and its *N*-vinyl derivative being isolated to indicate a reductive elimination of the nitro group.[33]

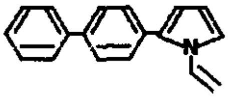
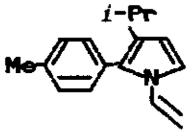
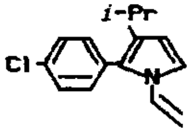
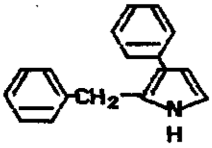
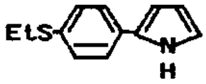
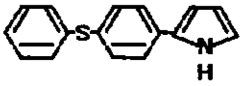
Oxime of 1-methyl-2-acetylpyrrole (**31**) reacts with acetylene under pressure (KOH/DMSO, 10 atm, 70°C, 3 h) to form 2-(1-methyl-2-pyrrolyl)pyrrole (**33**) and its vinyl derivative (**34**) in 35 and 7% yields, respectively (Scheme 15).[37] The reaction is accompanied by regeneration of 1-methyl-2-acetylpyrrole (**35**) and the polymer formation.



Scheme 15

The pyrrole (**34**) was isolated in 40% yield as the reaction temperature was increased to 90°C, other conditions keeping equal. The reaction is retained at the step of the *O*-vinyl oxime (**32**) formation (41% yield) when carried out

Table 2. New Syntheses of Arylpyrroles (KOH, 10-12 atm C_2H_2)[32]

Pyrrole	Reaction temp. (°C)	Reaction time (h)	Yield (%)
	100	3.0	69
	100	3.0	75
	100	3.0	76
	110	3.0	34[a]
	96	5.0	47[b,c]
	96	5.0	48[b,c]

[a] LiOH as a catalyst employed.

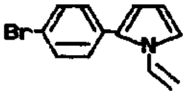
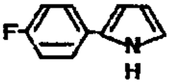
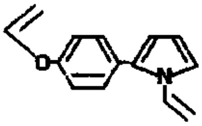
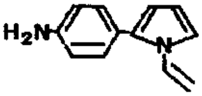
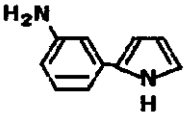
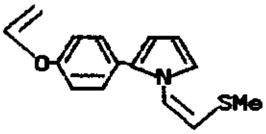
[b] The synthesis carried out at atmospheric pressure.

[c] Earlier prepared by the vinyl chloride version of the Trofimov reaction.[34]

at atmospheric pressure (80°C, 7 h, the **31**:KOH molar ratio 0.4), the yield of **33** being but 11%.

In prolongation of the systematic study[38-41] of the pyrrolylindoles synthesis by the Trofimov reaction, the latter was recently again confirmed to be an universal tool for the preparation of 2-pyrrolylindoles (Scheme 16).[12]

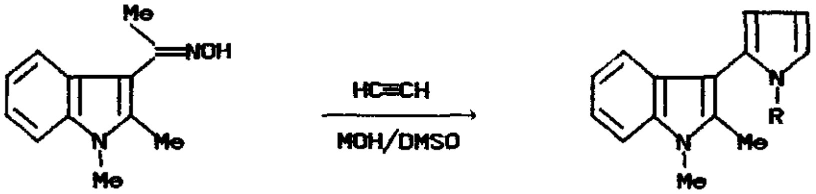
Table 3. Synthesis of Arylpyrroles with Reactive Substituents
(KOH, 12 atm C_2H_2)

Pyrrole	Reaction temp. (°C)	Reaction time (h)	Yield (%)
	90	3.0	35
	90	2.0	11
	100	3.0	27[a]
	70	3.0	30
	90	3.0	19
			0.01[b]

[a] With 10 atm C_2H_2.

[b] A side product from the synthesis with 4-hydrophenyl methyl ketoxime.[33,35]

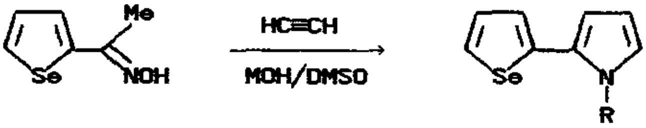
The pyrrolization of methyl 2-selenienyl ketoxime (**36**) under the action of acetylene (atmospheric pressure, KOH/DMSO, the KOH:**36** molar ratio 1.8) has



R = H, CH_2=CH

Scheme 16

been studied (Scheme 17) and the corresponding pyrroles (**37**a,b) have been isolated in 10 and 20% yield, respectively, when the reaction was carried out at 95-97°C for 5 h.[43]



36

37a,b

Scheme 17

Noteworthy, that the total yields of 2-(2-furyl)- and 2-(2-thienyl)- pyrroles from the oximes of 2-acetylfurane and 2-acetylthiophene, *i.e.*, from the ketoximes analogous to **36**, under similar conditions reach 80-90%.[11,14,16]

As the reaction temperature increases, the yield of **37a,b** as well as the amount of the recovered ketoxime (**36**) drop sharply (Table 4).

The starting ketoxime (**36**) was a ~1:1 mixture of *sin* and *anti* isomers and at 95-97°C the latter reacted preferably to enrich the recovered sample with the *sin* isomer up to 77%, being in accordance with the data on pyrrolization of methyl 2-benzimidazolyl ketoxime.[44]

The ^1H nmr spectra of the pyrroles (**37a,b**) show a remarkable down-field shift (0.2-0.5 ppm) of pyrrolic and vinylic protons as compared with those

Table 4. Pyrrolization of Methyl-2-selenienyl Ketoxime
(KOH/DMSO, atmospheric pressure)

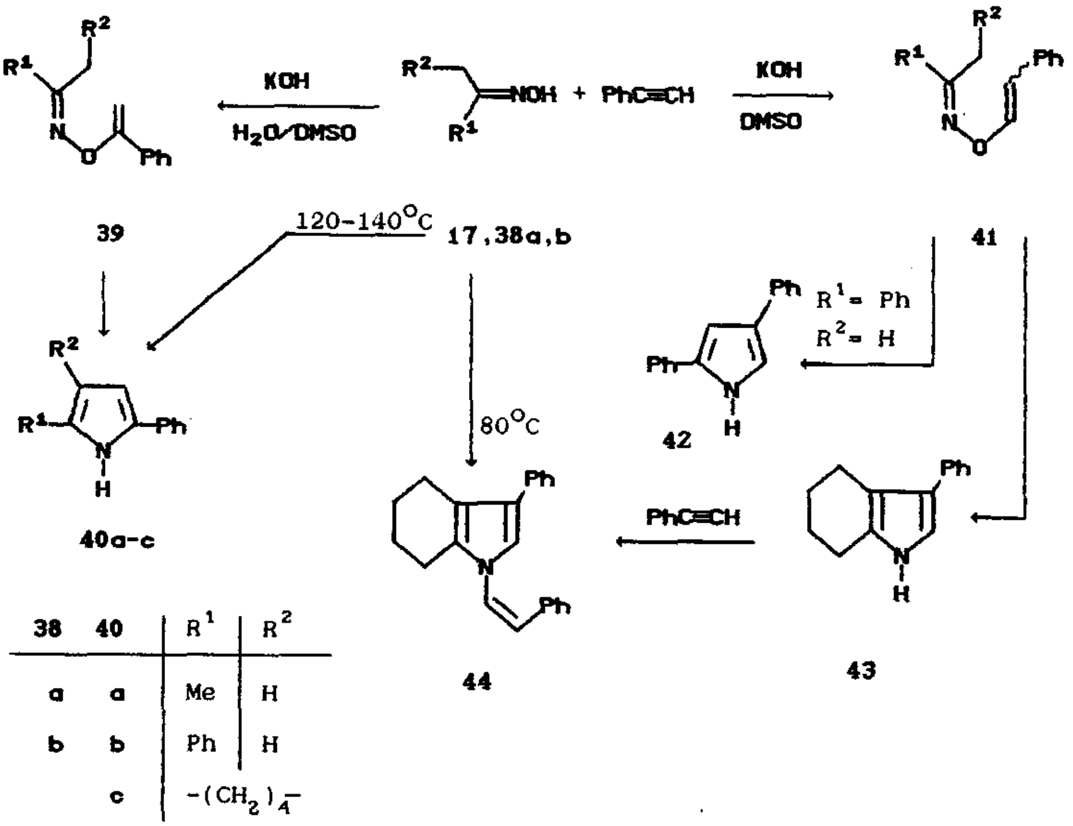
Reaction temp. (°C)	Reaction time (h)	Yield (%)		Recovery of **36** (%)
		37a	**37b**	
95-97	5	10	2	55
110	4	8	1	29
120	10	traces		traces

of other 1-vinylpyrroles[14,16] which implies a strongly π-electron displacement towards the selenophene nucleus. In the uv spectra of 2-(2-furyl)-, 2-(2-thienyl)- and 2-(2-selenienyl)pyrroles, the bathochromic shift of the longer wave band in the same order, in consistence with the polarizability of the molecules, is observed (287, 305, and 317 nm).[43]

2.4. Reactions of Ketoximes with Substituted Acetylenes

The reaction of ketoximes with substituted acetylenes was so far reported only in a limited number of papers, most of which were discussed in the monograph.[14] In some cases, *e.g.*, with cyanoacetylene[45] or diacetylene,[46,47] the pyrrole formation was not observed, although the corresponding *O*-vinyl oximes, commonly obligatory intermediates of the ketoxime-based pyrrole synthesis, were isolated.

Oximes of acetone (**38a**) and acetophenone (**38b**) were first reported to be capable of reacting with phenylacetylene in the KOH/DMSO system at 120-140°C to give α-phenylpyrroles (**40a,b**) in 21 and 15% yields, respectively (Scheme 18).[48]



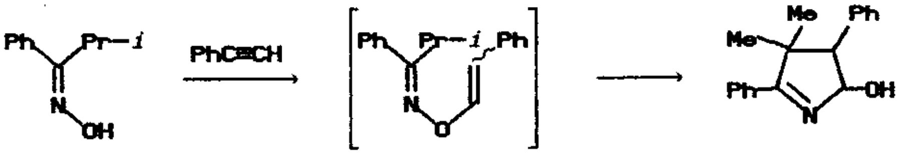
38	40	R^1	R^2
a	a	Me	H
b	b	Ph	H
	c	$-(CH_2)_4-$	

Scheme 18

Later,[49] 2,4-diphenylpyrrole (**42**) was obtained in 17% yield by heating *Z*-*O*-(2-phenylvinyl)acetophenone oxime (**41**, R^1= Ph, R^2= H) up to 105°C within 30 min in the KOH/DMSO system. The starting *O*-vinyl oxime (**41**) was prepared in advance by addition of the ketoxime (**38b**) to phenylacetylene (KOH/DMSO, 20°C, 50 h) in 70% yield (based on the oxime consumed) at the 42% conversion of **38b**.

Recently,[50] the major product of the condensation of cyclohexanone oxime (**17**) with phenylacetylene at 80°C (KOH/DMSO) was shown to be *Z*-[1-(2-phenylvinyl)]-3-phenyl-4,5,6,7-tetrahydroindole (**44**) isolated in 42% yield, the corresponding non-vinylated pyrrole (**43**) being the obligatory precursor. Unexpectedly, in the presence of water (5%) at 96°C the same reaction affords 2-phenyl-4,5,6,7-tetrahydroindole (**40c**) in 22% yield, thus indicating that small amounts of water in the reaction mixture favors the formation of *O*-(1-phenylvinyl) ketoximes (**39**) rather than their β-isomers (**41**).

Isopropyl phenyl ketoxime (**45**) with phenylacetylene at ambient temperature (KOH/DMSO, two-fold molar excess of KOH, 15 days) forms 3,3-dimethyl-2,4-diphenyl-5-hydroxypyrroline (**47**) in 7% yield, apparently *via* *O*-vinyl oxime **46** (Scheme 19).[50]

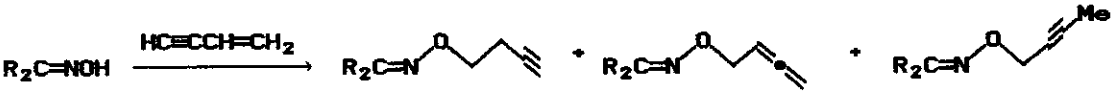


45 **46** **47**

Scheme 19

Vinylacetylene reacts with ketoximes, instead of the expected vinylpyrroles, in MOH/DMSO systems (M = Li, K) at 60-75°C to give the mixtures of *O*-3- and *O*-2-butynyl (**48**,**50**) and *O*-2,3-butadienyl (**49**) ketoximes in a total yield up to 50% (Scheme 20).[51,52] Initially, the oximate anions add exclusively to the double bond of vinylacetylene to form **48**, which then undergo a facile prototropic isomerization to **49** and **50**.

Propargyl ethers (**51**) add ketoximes, under conditions normally leading to pyrroles (KOH/DMSO, 110°C, 7 h) to form neither the expected pyrroles (**53**) nor their precursors, *O*-vinyl ketoximes (**52**). The only isolated products (in small yields, 9-12%) are *E*-*O*-(3-alkoxy-2-propenyl) oximes (**54**) (Scheme 21).[53]

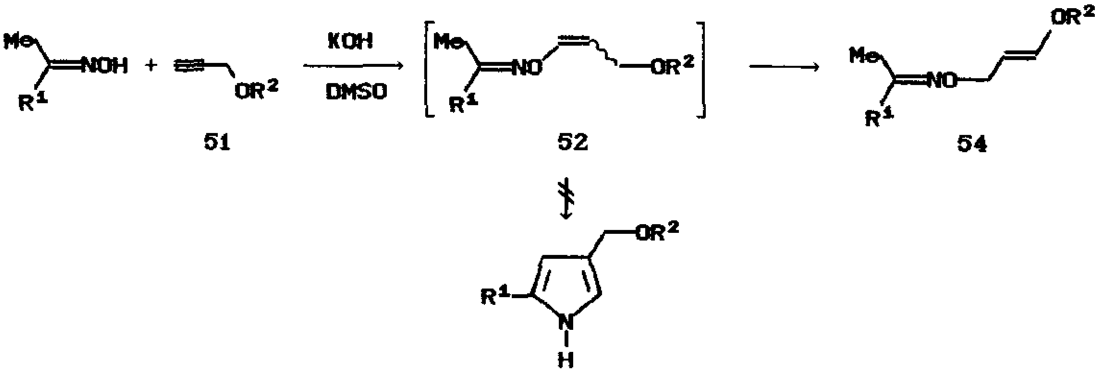


48 **49** **50**

R = Me, R–R = $(CH_2)_4$

Scheme 20

Apparently, the intermediate *O*-vinyloximes (**52**) undergo a fast stereospecific prototropic isomerization, which is likely due to a higher conjugation of the double bond with the alkoxy group rather than with iminoxy group.

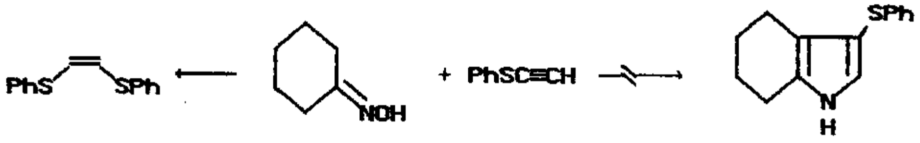


51 **52** **54** **53**

R^1 = Ph, 2-thienyl; R^2 = Et, *n*-Pr

Scheme 21

The attempted synthesis of 3-phenylthio-4,5,6,7-tetrahydroindole (**55**) according to Scheme 22 (KOH/DMSO/Et_2O, 25-30°C, 2.5 h) gave 1,2-diphenylthioethene (**56**) in 40% yield.[54]

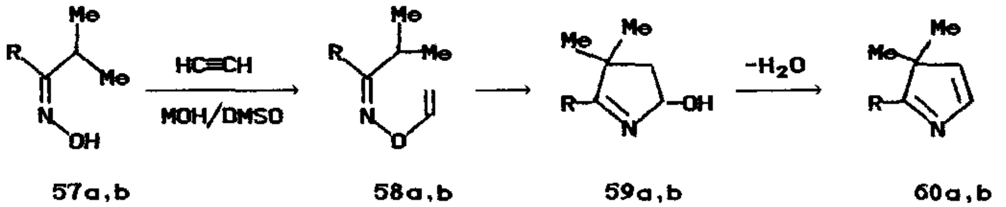


56 **55**

Scheme 22

2.5. Synthesis of 3*H*-Pyrroles

3*H*-Pyrroles were shown[55] to be intermediates in the synthesis of pyrroles from ketoximes and acetylene. In the case of the secondary alkyl adjacent to the oxime function, 3*H*-pyrroles can be isolated,[19,55] thus promising a convenient route to the heretofore inaccessible and highly reactive nonconvenient route to the heretofore inaccessible and highly reactive non-aromatic pyrrole isomers. Recently,[56] this opportunity has been further developed with isopropyl phenyl and isopropyl 2-thienyl ketoximes and the corresponding 3*H*-pyrroles (**60a,b**) have been synthesized in 53 and 43% maximal yields, the latter being referred to the reacted ketoxime (**57b**) (Scheme 23).



R = Ph (**a**), 2-thienyl (**b**)
M = Na, K

Scheme 23

The yield of the 3*H*-pyrroles (**60**) turned out to be substantially dependent on both the structure of the substituent R and the reaction conditions. Generally, the ketoxime (**57a**) reacts with acetylene at 100°C (atmospheric pressure, the **57a**:KOH molar ratio 1:2, 3 h) much easier than its 2-thienyl analog (**57b**). For example, when the yield of **60a** was determined as much as 42%, the yield of **60b**, under the same conditions, remained on the level of 4% only, even for a longer reacting time (5 h). The highest yield of **60a** (53%) was attained under the following conditions: atmospheric pressure of acetylene, 90°C, the ketoxime:KOH molar ratio 1:1, 4 h. In the case of the ketoxime (**57b**), the best result (43% yield based on the reacted ketoxime) has been gained with Al_2O_3 as an additive (7% of the KOH mass, atmospheric pressure, 100°C, 5 h), which seems to increase the basicity of the reaction mixture by its complexing with KOH and desiccating activity. Under pressure (12 atm, 100°C) the reaction is accompanied by polymerization of both the intermediates (**58**,**59**) and the products that decreases the yield of 3*H*-pyrroles. At a lower temperature, the reaction of the ketoxime (**57a**) with acetylene can be stopped at the intermediate stages: *e.g.*, at 40°C the major product is *O*-vinyl oxime (**58a**) (37% yield), whereas at 50°C, 3,3-dimethyl-5-hydroxy-2-phenylpyrroline (**59a**) is mostly formed (23% yield).

At atmospheric pressure with the NaOH/DMSO system (100°C) the hydroxypyrroline (**59a**) can be prepared in nearly the same yield.

As shown by glc monitoring of the reaction progress (Figure), the ketoxime (**57a**) almost disappears from the crude product within 4 h, while the intermediate *O*-vinyl oxime (**58a**) immediately rearranges into the hydroxypyrroline (**59a**) not reaching a considerable concentration. The latter, eliminating a molecule of water, transforms into 3*H*-pyrrole (**60a**), which becomes detectable ~40 min after the reaction starts and by the end of the reaction its content in the crude product reaches 70%.[56]

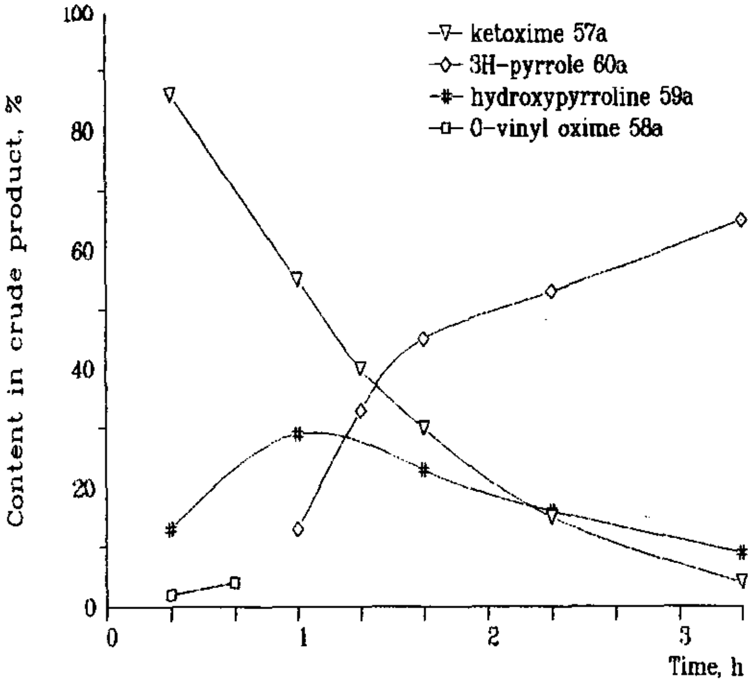
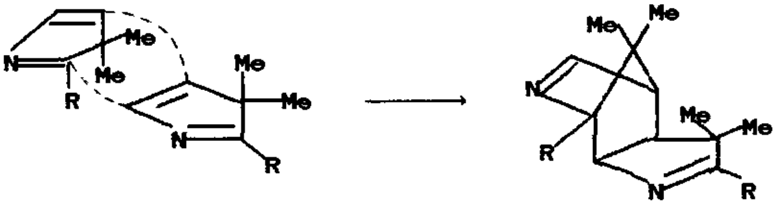


Figure. Glc monitoring of the 3*H*-pyrrole (**60a**) formation (atmospheric pressure, 92-95°C, the **57a**:KOH molar ratio 1:1).[56]

When stored during 9-10 months in a sealed ampoule at 5-7°C, the 3*H*-pyrroles (**60a,b**) dimerize regio- and stereoselectively in a Diels-Alder fashion (Scheme 24)[57] to afford the representatives of a new bridgehead system 3,3,10,10-tetramethyl-4,7-diphenyl- [or 4,7-(di-2-thienyl)]-5,8-diazotricyclo[4.3.1.0^{2,6}]deca-4,8-dienes (**61a,b**) in 20-23% yield.



60a,b **61a,b**

R = Ph, 2-thienyl

Scheme 24

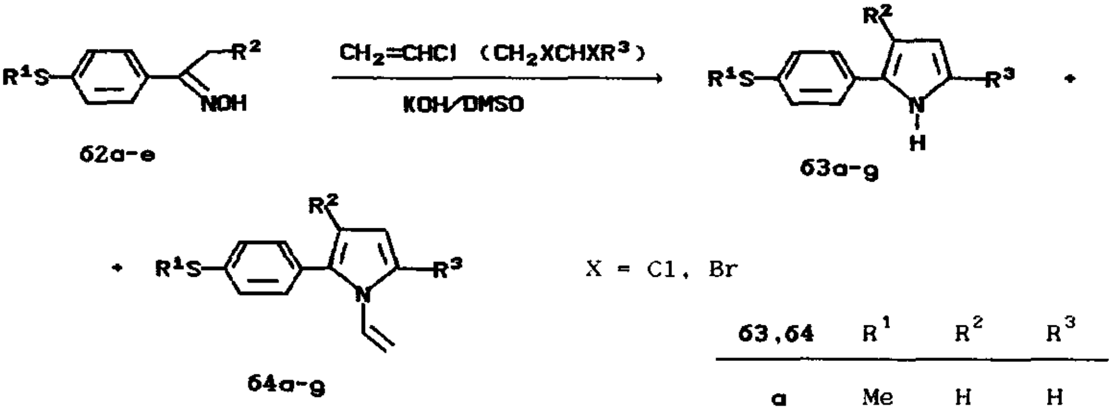
This condensation provides a simple approach to earlier unknown partially reduced pyrrolopyridines.

2.6. Vinyl Halides and Dihaloalkanes as Acetylenic Equivalents

The "acetylene-free" versions of the Trofimov reaction keep further developing for the latest years. As acetylenic equivalents ("cryptoacetylenes"), vinyl halides or dihaloalkanes are commonly employed.

2-(4-Alkylthiophenyl)-3-methyl- or -(3,5-dimethyl)pyrroles were synthesized from ketoximes and vinyl chloride or 1,2-dichloroethane, 1,2-dibromoethane and 1,2-dibromopropane (KOH/DMSO, atmospheric pressure, 120-140°C) in a yield up to 62% (Scheme 25).[58]

For example, the pyrrole (**63b**) was prepared in 62% yield, when the reaction was carried out with a three-fold molar excess of 1,2-dibromoethane and ten-fold molar excess of KOH relative to the ketoxime (**62b**) (130°C, 4 h, the ketoxime (**62b**):DMSO ratio ~1:10), the corresponding 1-vinylpyrrole (**64b**) being detectable in the reaction mixture as a trace only. Similarly, from the ketoxime (**62c**) with a three-fold excess of dichloroethane at 120^{o}C the pyrrole (**63c**) is formed in 61% yield.



X = Cl, Br

62	R^1	R^2
a	Me	H
b	Et	H
c	*i*-Pr	H
d	Me	Me
e	Et	Me

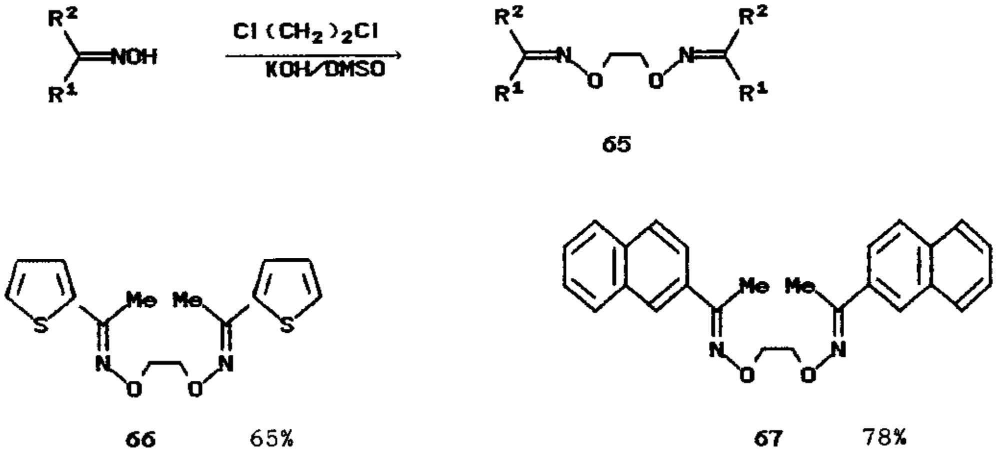
63,64	R^1	R^2	R^3
a	Me	H	H
b	Et	H	H
c	*i*-Pr	H	H
d	Me	Me	H
e	Et	Me	H
f	Me	H	Me
g	Et	H	Me

Scheme 25

To ensure reasonable yields of the pyrroles one should gradually add 1,2-dihaloalkanes to the suspension consisting of KOH excess, ketoxime and DMSO.

A 5-6-fold excess of vinyl chloride is recommended[58] to prepare a mixture of pyrroles (**63d,e**) and (**64d,e**) in a total yield of 50%. The synthesis of the 5-methylpyrroles (**63f,g**) in 45-48% yields has been accomplished[58] with a 3-fold excess of 1,2-dibromopropane and up to the 20-fold excess of finely dispersed KOH (130-140^{o}C, 1-5 h), the ketoxime:DMSO mass ratio being 1:20.

In this case, side products of the reaction of the ketoximes with 1,2-dihaloethanes, 1,2-di(arylideniminoxy)ethanes (**65**) (Scheme 26) were reported[59] to be formed in negligible amounts, while, under special conditions [80-100°C, 2-3 h, the ketoxime:dichloroethane:KOH molar ratio 1:(2-5):(5-8)] and with some particular ketoximes, the yields of such diethers can be as high as 65% (for **66**) and 78% (for **67**).[60]

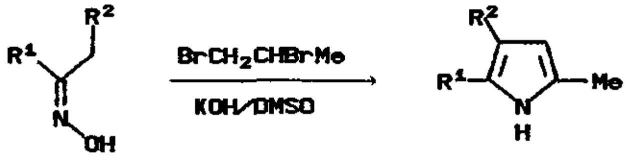


Scheme 26

Vinyl chloride was used to prepare the pyrroles (**29a,b,e**) in a yield of 50%, the yield of the corresponding *N*-vinylpyrroles (**30a,b,c**) being 6-7% (atmospheric pressure, 130°C, 3.5 h, the ketoxime:$CH_2=CHCl$:KOH molar ratio 1:5:6, the ketoxime:DMSO mass ratio 1:12.5).[31]

From the ketoximes (**68a-c**) and 1,2-dibromopropane the corresponding 5-methylpyrroles (**69a-c**) were synthesized in 21-56% yield (Scheme 27) (140°C, the ketoxime:$BrCH_2CHBrMe$:KOH molar ratio 1:5:20, the ketoxime:DMSO mass ratio 1:30).[61] The most probable reaction sequence is as follows: the elimination of HBr from 1,2-dibromopropane to furnish methylacetylene and allene, which then add the ketoximes (**68**) to form *O*-vinyl oximes (**70**), rearranging to the pyrroles (**69**) (Scheme 28).

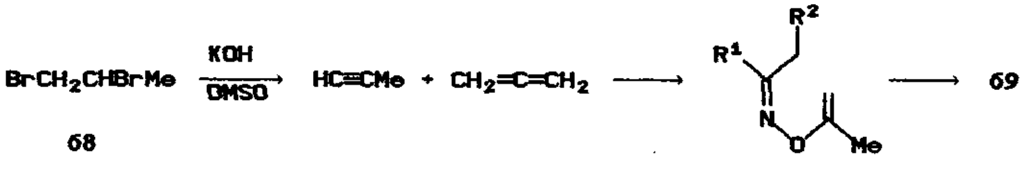
Apparently, the industrially available methylacetylene-allene mixture, a large-volume side product of oil and natural gas processing, may also be suitable for the preparation of 5-methylsubstituted pyrroles.



68a-c **69a-c**

69	R^1	R^2	Yeld (%)
a	Ph	H	56
b	4-FC_6H_4	H	21
c	$-(CH_2)_4-$		42

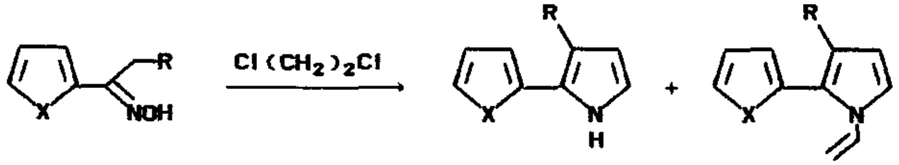
Scheme 27



68 **70**

Scheme 28

2-(2-Furyl)- and 2-(2-thienyl)pyrroles (**71**) were synthesized in satisfactory yields (Table 5), using 1,2-dichloroethane instead of free acetylene (Scheme 29).[62] The best yields of the corresponding *N*-vinyl derivatives (**72**) are in a range of 15-20%.



71 **72**

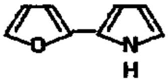
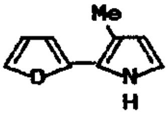
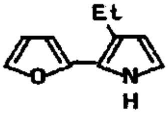
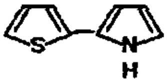
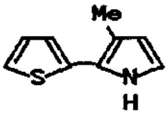
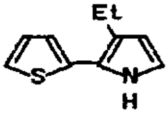
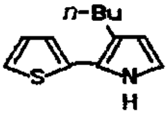
X = O, S; R = Me, Et, *n*-Bu

M = Li, Na, K

Scheme 29

The reaction of alkyl 2-furyl or 2-thienyl ketoximes was shown[62] to proceed *via* the intermediate *O*-2-chloroethyl oximes (**73**) and *O*-vinyl oximes (**74**),

Table 5. Synthesis of 2-(2-Furyl)- and 2-(2-Thienyl)pyrroles Using 1,2-Dichloroethane ($120^{\circ}C$)[62]

Pyrrole (**71**)	Oxime:$Cl(CH_2)_2Cl$:MOH ratio[a], mol	Reaction time (h)	Yield (%)
	1:2:10 (K)[b]	7	47[c]
	1:2:10 (Na)	6	30[d]
	1:3:7 (Na)	9	25
	1:2:10 (K)	7	54
	1:2:7 (Na)	9	38
	1:2:7 (Na)	7	34[c]
	1:2:7 (Na)	6.5	42

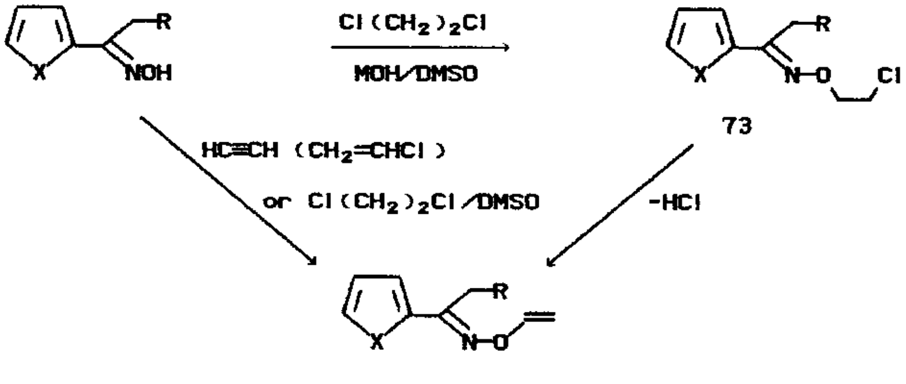
[a] The oxime:DMSO mass ratio 1:10

[b] In the brackets, the metal of MOH is given.

[c] Water (5% of the DMSO mass) was added

[d] The temperature range was 125-130°C

the latter being formed particularly in the presence of water and with LiOH or NaOH (Scheme 30). *O*-(2-Chloroethyl) methyl (2-thienyl) ketoxime (**73**, X = S, R = H) was isolated in 24% maximal yield (KOH/DMSO, 110°C, 3 h). The best yield (43%) of *O*-vinyl methyl (2-thienyl) ketoxime (**74**, X = S, R = H) was obtained when the LiOH/DMSO system with 10% of H_2O was employed (100°C, 4 h).[62]



74

X = O, S; R = H, Me, Et, *n*-Bu

M = Li, Na, K

Scheme 30

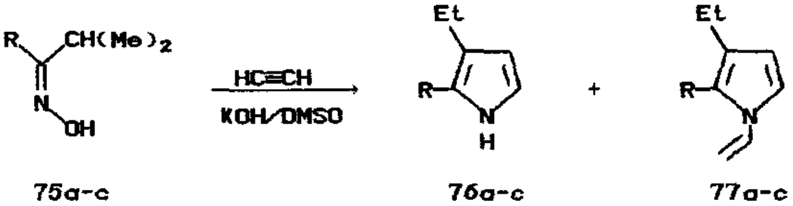
The formation of side 1,2-di(heteroarylalkylideniminoxy)ethanes of type **65** was observed also in this case.[62]

2.7. Side Products

Normally, just few side products in small amounts are detectable in the reaction mixtures obtained from ketoximes and acetylene with MOH/DMSO systems. Among them, 1,1-di(pyrrolyl)ethanes[63] and 1-(2-methylthiovinyl)pyrroles[33,35] were earlier reported, the yield of each being on the level of 0.1% under normal conditions. Recently,[64] the formation of di(1,2,3,4-tetrahydro-2,4,5-trimethylpyrrolo[1,2-*c*]pyrimidin-7-yl)methane from oxime of *1,3,5-trimethylpiperidin-4-one* and acetylene in the presence of the KOH/DMSO pair has been detected.

Pyridines[65,66] and acetylenic alcohols[67] are not typical side products, since they are produced from ketoximes and acetylene under special conditions: *e.g.*, pyridines are formed in a yield up to 30% in water with KOH at 200-220°C under acetylene pressure of 20-30 atm, whereas the formation of acetylenic alcohols is observed, when the reaction is carried out in aqueous DMSO at 100-140°C with MOH (M = Li, Na, K, Rb).

3-Ethylpyrroles (**76**) and their *N*-vinyl derivatives (**77**) were reported[68] to be formed in the synthesis of 3*H*-pyrroles from isopropyl ketoximes (**75**) (Scheme 31). These pyrroles were isolated from the reaction mixture in a yield up to 8%, along with the expected *O*-vinyl ketoximes, hydroxypyrrolines, and 3*H*-pyrroles, when the ketoximes (**75**) reacted with acetylene in the KOH/DMSO system (10-12 atm or atmospheric pressure, 90-100°C).



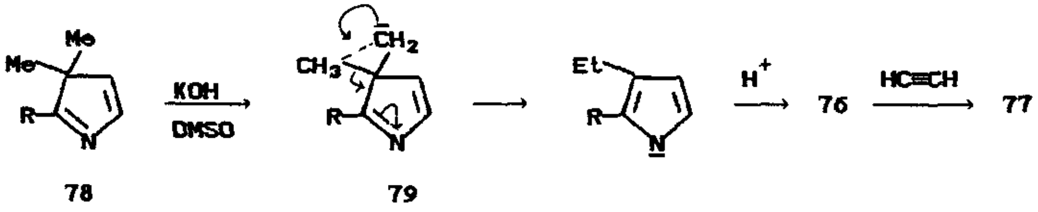
R = Me (**a**), Ph (**b**), 2-thienyl (**c**)

Scheme 31

The rearrangement was assumed to occur in the carbanion (**79**), resulted from deprotonation of the corresponding 3*H*-pyrrole (**78**) under the action of the super base KOH/DMSO (Scheme 32).[68]

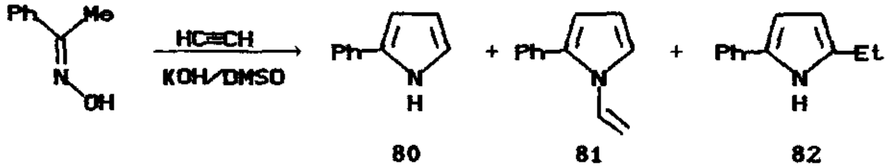
A driving force of the methyl transfer is a considerable energy difference between non-aromatic (**78**) and aromatic (**76**,**77**) systems.

2-Ethyl-5-phenylpyrrole (**82**) in a negligible amount (0.3% yield) has been isolated (tlc, Al_2O_3, hexane-Et_2O 3:1) from the reaction of acetophenon



Scheme 32

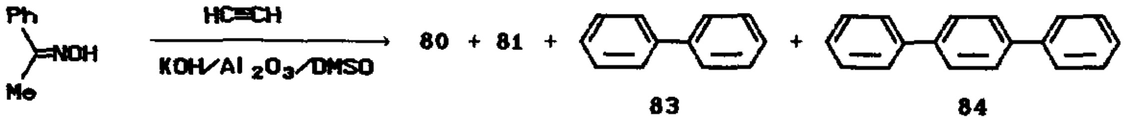
oxime with acetylene (100-110°C) along with the major products 2-phenyl (**80**)- and 1-vinyl-2-phenylpyrroles (**81**) (Scheme 33).[69]



Scheme 33

At 120°C in the presence of Al_2O_3 (20% of the ketoxime mass), the yield of the side pyrrole (**82**) increases up to 1.6%. This unexpected α-ethylation was supposed to result from the reductive decomposition of the 1,1-di(2-phenyl-5-pyrrolyl)ethane. The side product of the latter type were earlier identified[63] in this reaction and their transformation to α-ethylpyrroles was also known.[70]

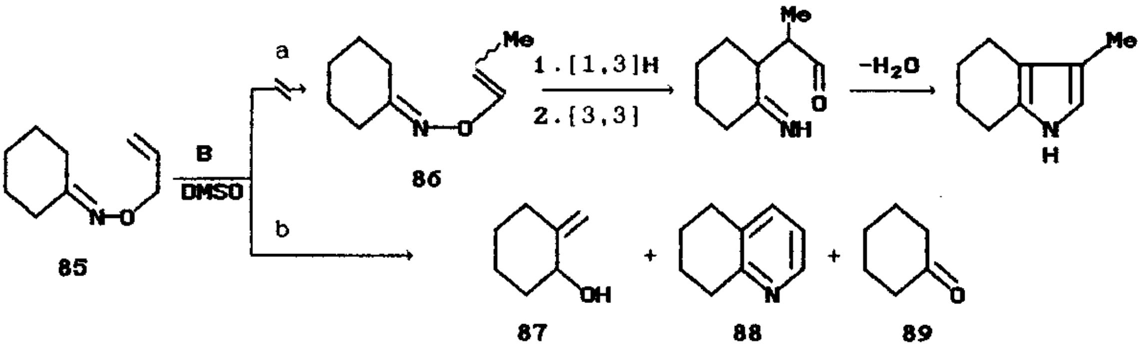
The synthesis of pyrroles from alkyl phenyl ketoximes and acetylene (80-120°C, KOH/DMSO) was shown to be accompanied by a process leading to small amounts (~1%) of diphenyl (**83**) and *p*-terphenyl (**84**), the latter being isolated (Al_2O_3, hexane-EtOH 50:1) in 0.3% yield, from the reaction of acetophenone oxime with acetylene (KOH/Al_2O_3/DMSO, 120°C, atmospheric pressure, the ketoxime:KOH molar ratio 1:2) (Scheme 34).[71]



Scheme 34

3. *O*-Allyl Cyclohexanone Oxime Transformation

The pyrrole synthesis from ketoximes and acetylene in the presence of super bases involves a [3,3]-sigmatropic shift in the intermediate *O*-vinyl oximes.[11,14,16] Under the conditions commonly employed for the synthesis, prototropic displacements of double bonds occur readily.[5] Therefore, the transformation of available *O*-allyl ketoximes into pyrroles according to the pathway "*a*" (Scheme 35) might be considered as probable, although, upon non-catalytic pyrolysis, *O*-allyl ketoximes were known[72-74] to undergo the [2,3]-sigmatropic shift to form nitrones, isoxazolidines and pyridines. Unexpectedly, major products of the reaction of *O*-allyl ether of cyclohexanone oxime (**85**) with KOH or *t*-BuOK in DMSO (50-140°C, 1-6 h) turned out to be 2-methylenecyclohexanol (**87**), tetrahydroquinoline (**88**) and cyclohexanone (**89**) (Scheme 35)[75,76], *i.e.*, the reaction follows the pathway "*b*".



B = KOH, *t*-BuOH

Scheme 35

A typical composition (**glc**, %) of the extractable portion of the reaction mixture (100°C, 4 h) is as follows[75]: **87**, 50-70; **88**, 20-30; **89**, 5-10. It has been concluded[76] that the prototropic shift of the double bond of *O*-allyl oximes of type (**85**) to form 1-propenyl ethers (**86**) is prevented by an apparently strong repulsion of the lone electron pairs of the nitrogen and oxygen atoms destabilizing the initial carbanion. This is in accordance with the synthesis of *O*-allyl oximes (**54**), instead of the expected pyrroles (**53**), from ketoximes and propargyl ethers (**51**) (Scheme 21), where the forming double bond is readily shifted from the =NO moiety towards the alkoxy group.

4. *N*-Vinylation

N-Vinylation of the forming pyrroles normally occurs during the reaction of ketoximes with acetylene in the KOH/DMSO system. With excess acetylene, particularly under pressure, *N*-vinylpyrroles can cleanly be prepared. This process is progressively inhibited by increasing concentration of water in the course of the pyrrole ring building due to the dehydration of the intermediate hydroxypyrroline.[2,8,11,14,16] This is why, for the preparation of *N*-vinylpyrroles, it is recommended[2,8,11,14,16] to use large amounts of KOH (which dries the reaction mixture and keeps a high basicity level).

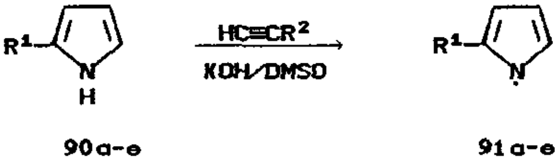
On the contrary, for selective preparation of 1*H*-pyrroles, an optimal water additive (~5% of the total mass) to the reaction mixture is often used.[2,8,11,14,16] Distillable pure 1*H*-pyrroles can also be isolated by thiylation of crude pyrroles contaminated with 1-vinylpyrroles to transform the latter into higher boiling 1-(2-organylthioethyl)pyrroles, which do not distil off together with 1*H*-pyrroles as 1-vinylpyrroles do.

Now 1-vinylpyrroles are considered as the pyrroles with a protected nitrogen atom and several deprotecting procedures, including those *via* 1-(2-phenylthioethyl) derivatives, have been developed.[77]

Pure 1-vinylpyrroles can readily be prepared by vinylation of mixtures consisting of 1*H*- and 1-vinylpyrroles with acetylene under atmospheric or elevated pressure (KOH/DMSO, 80-100 $^{\circ}$C). Sometimes, vinylation under atmospheric pressure proves to be not only safer but also more effective due to a less resinification and simpler experimental procedure.[16]

The structural effects on the rate of the pyrrole vinylation have been *studied*[16,78] and the facts implying the operation of a one-electron channel for the nucleophilic addition of pyrroles to the triple bond have been revealed.[16,78-81] Since the results[78-81] have already been digested in[16], we dwell here just on the recent continuation[82] of the study of radical processes during the vinylation of pyrroles in the KOH/DMSO system.

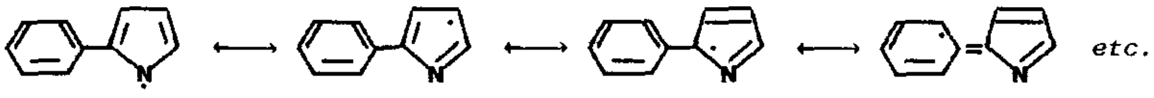
Unlike the vinylation of 4,5,6,7-tetrahydroindole, where the corresponding tetrahydroindolyl radicals were detected[81] with the help of 2-methyl-2-nitrosopropane (*t*-BuNO), in the vinylation of 2-aryl- and 2-heteroarylpyrroles, no nitrogen-centered radicals have been trapped.[82] Instead, for the 2-arylpyrroles, other radical adducts with *t*-BuNO have been registered, whereas, in the case of 2-(2-furyl)- and 2-(2-thienyl)pyrroles no adducts with *t*-BuNO have been observed. Also, unlike 4,5,6,7-tetrahydroindole, the 2-aryl- and 2-heteroarylpyrroles, when vinylated with or without *t*-BuNO give in esr spectra a singlet in the g-factor region of 2.0036-2.0042 with the width of 0.6-0.7 mT, which has been attributed to the pyrrole radicals (**91**) (Scheme 36).



R^1 = Ph (**a**), 4-ClC$_6$H$_4$ (**b**), 4-MeC$_6$H$_4$ (**c**), 2-furyl (**d**), 2-thienyl (**e**)
R^2 = H, Ph

Scheme 36

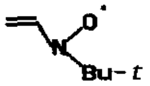
These radicals are not uptaken by the spin trap, likely because of their relative stability and steric inaccessibility of the radical center in the most populated structure (**92**) (Scheme 37).



92

Scheme 37

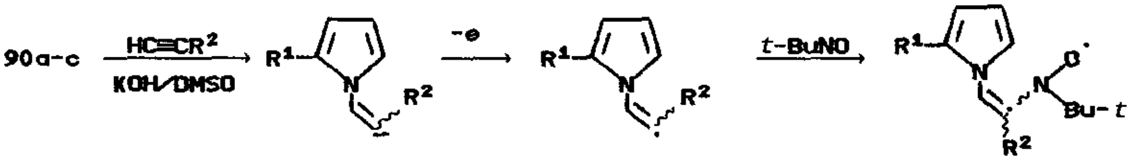
The esr spectra of the spin adducts of the 2-arylpyrroles (**90a-c**) vinylated with acetylene or phenylacetylene, exhibit a superposition of two triplets of doublets, one of which, judging from the literature data, has been assigned to the vinyl-*t*-butylnitroxyls (**93**, **94**).



93

94

The second triplet has been attributed to the spin adducts (**97**) formed from *N*-vinylpyrrolic radicals(**96**)and *t*-BuNO (Scheme 38).



95 **96** **97**

97, R^2 = H

R^1	^aN (mT)	^aH (mT)
Ph	1.289	1.002
4-ClC_6H_4	1.178	1.178
4-MeC_6H_4	1.155	1.155

97, R^2 = Ph

R^1	^aN (mT)	^aH (mT)
Ph	1.500	0.333
4-ClC_6H_4	1.511	0.289
4-MeC_6H_4	1.466	0.373

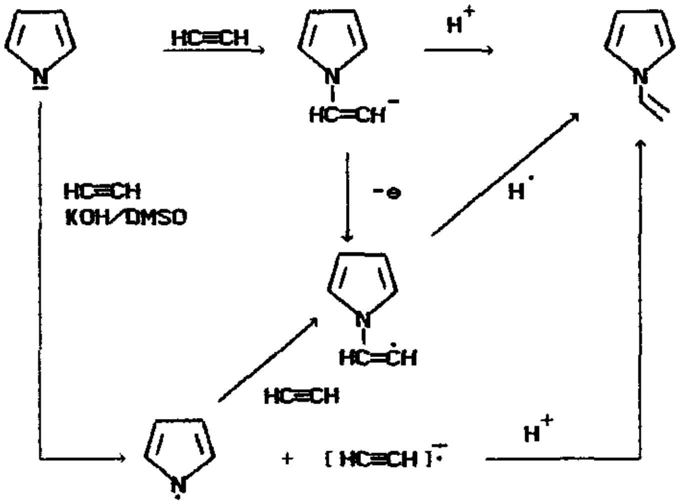
Scheme 38

The radical (**96**) can be generated by not only oxidation of the vinylic carbanions (**95**) (Scheme 38), but also by the addition of pyrrolyl (**91**) to acetylenes:

$$\mathbf{91} + HC{\equiv}CR^2 \longrightarrow \mathbf{96}.$$

The facts that *t*-BuNO does not trap any radicals during vinylation of the pyrroles (**90d,c**) and that the signal intensity of the pyrrolic radicals (**91d,c**) increases in the presence of *t*-BuNO, are rationalized by an easier oxidation of these radicals as compared with their addition to the spin trap.[81]

Thus, according to the structure of the trapped radicals the vinylation of pyrroles in the KOH/DMSO system follows Scheme 39.



Scheme 39

The contribution of the anionic and free radical channels to the total vinylation process should apparently depend on the structure of pyrrole and acetylene substituents as well as on the reaction conditions.

REFERENCES

1. G.P. Bean, 'The Chemistry of Heterocyclic Compounds, Vol. 48, Part 1, Pyrroles,' ed. by R.A. Jones, Wiley, New York, 1990, pp. 105-294.
2. B.A. Trofimov and A.I. Mikhaleva, *Khim. Geterotsikl. Soedin.*, 1980, 1299 (*Chem. Abstr.*, 1981, **94**, 47025).
3. B.A. Trofimov, *Usp. Khim.*, 1981, **50**, 249.
4. B.A. Trofimov, A.I. Mikhaleva, and L.V. Morozova, *Usp. Khim.*, 1985, **54**, 1034 (*Chem. Abstr.*, 1985, **103**, 123936).
5. B.A. Trofimov, *Zh. Org. Khim.*, 1986, **22**, 1991.
6. B.A. Trofimov, *Z. Chem.*, 1986, **26**, 41.
7. B.A. Trofimov and A.I. Mikhaleva, *Khim. Geterotsikl. Soedin.*, 1987, 1299 (*Chem. Abstr.*, 1988, **109**, 6333).
8. B.A. Trofimov, *Usp. Khim.*, 1989, **58**, 1703 (*Chem. Abstr.*, 1990, **113**, 6046).
9. L.N. Sobenina, A.I. Mikhaleva, and B.A. Trofimov, *Khim. Geterotsikl. Soedin.*, 1989, 291 (*Chem. Abstr.*, 1989, **111**, 173920).
10. L.N. Sobenina, A.I. Mikhaleva, and B.A. Trofimov, *Usp. Khim.*, 1989, **58**, 275 (*Chem. Abstr.*, 1989, **111**, 57423).
11. B.A. Trofimov, *Adv. Heterocycl. Chem.*, 1990, **51**, 178.
12. B.A. Trofimov, 'Heteroatomic Derivatives of Acetylenes. New Polyfunctional Monomers, Reagents and Intermediates' (in Russian), Nauka, Moscow, 1981 (*Chem. Abstr.*, 1982, **96**, B 68296).
13. B.A. Trofimov, N.I. Golovanova, N.I. Shergina, A.I. Mikhaleva, S.E. Korostova, A.N. Vasil'ev, and I.L. Anisimova, 'Atlas of Spectra of Aromatic and Heterocyclic Compounds' (in Russian), Vol. 21, Institute of Organic Chemistry Sib. Div. Akad. Nauk SSSR, Novosibirsk, 1981.
14. B.A. Trofimov and A.I. Mikhaleva, 'N-Vinylpyrroles' (in Russian), Nauka, Novosibirsk, 1984 (*Chem. Abstr.*, 1985, **102**, 203864).

15. B.A. Trofimov, L.N. Sobenina,and A.I. Mikhaleva, 'Uspekhi Sinteza Pirrolov' (in Russian), Itogi Nauki i Tekhniki, Organicheskaya Khimia, Vol. 7, Moscow, 1987.

16. B.A. Trofimov, 'The Chemisrty of Heterocyclic Compounds, Vol. 48, Pyrroles,' Part 2, ed. by R.A. Jones, Wiley, New York, 1992, pp. 131-298.

17. A.M. Vasil'tsov, E.A. Polubentsev, A.I. Mikhaleva, and B.A. Trofimov, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 1990, 864 (*Chem. Abstr.*, 1990, **113**, 58266).

18. B.A. Trofimov, A.M. Vasil'tsov, A.I. Mikhaleva, G.A. Kalabin, V.V. Shcherbakov, R.N. Nesterenko, E.A. Polubentsev, and K.D. Praliev, *Khim. Geterotsikl. Soedin.*, 1991, 1365.

19. T.N. Borisova, A.V. Varlamov, N.D. Sergeeva, A.T. Soldatenkov, O.V. Zvolinskii, A.A. Astakhov, and N.S. Prostakov, *Khim. Geterotsikl. Soedin.*, 1987, 973 (*Chem. Abstr.*, 1988, **108**, 167344).

20. N.S. Prostakov,A.V. Varlamov, T.N. Borisova, and N.D. Sergeeva, *Khim. Geterotsikl. Soedin.*, 1987, 1286 (*Chem. Abstr.*, 1988, **109**, 6472).

21. T.N. Borisova, A.E. Aliev, I.A. Stazharova, A.V. Varlamov, and N.S. Prostakov, II Vsesoyuznaya Konferentsiya po Khimii, Biokhimii i Farmakologii Proizvodnikh Indola, Tezisi Dokladov, Tbilisi, 1991, p. 24.

22. T.N. Borisova, A.E. Aliev, I.A. Stazharova, N.S. Prostakov, and A.V. Varlamov, *Khim. Geterotsikl. Soedin.*, 1991, 849.

23. T.N. Borisova, I.A. Stazharova, A.E. Aliev, N.S. Prostakov, and A.V. Varlamov, *Khim. Geterotsikl. Soedin.*, 1991, 1375.

24. A.E. Aliev, T.N. Borisova, I.A. Stazharova, A.A. Sinitsina, A.I. Mikaya, N.S. Prostakov, and A.V. Varlamov, *Khim. Geterotsikl. Soedin.*, 1992, 903.

25. A.M. Vasil'tsov, R.N. Nesterenko, and K.D. Praliev, V Vsesoyuznaya Konferentsiya po Khimii Azotsoderzhaschikh Geterotsikl. Soedin., Tezisi Dokladov, Tchernogolovka, 1991, p. 45.

26. I.E. Demidov, V.N. Buyanov, I.I. Levina, T.K. Efimova, T.A. Kozik, and N.N. Suvorov, 'Fiz. Khim. Problemi Khimicheskih Proizvodstv.' Moskovskii Khim. Tekhnologich. Institut, Moscow, 1990, pp. 182-183; *Ref. Zh. Khim.* 24Ж249 (1991).

27. I.E. Demidov, B.N. Buyanov, and N.N. Suvorov, 10 Molod. Konferentsiya po Sintet. i Prirod. Fiziol. Aktiv. Soed., Tezisi Dokladov, Erevan, 1990, p. 42.

28. A.M. Vasil'tsov, A.I. Mikhaleva, E.A. Polubentsev, and B.A. Trofimov, USSR Inventor's Sertificate N 1705284 A1 (1989), registered 1991, published 1992 (Russian Inventor's Bulletin N 2).

29. A.I. Mikhaleva, M.V. Sigalov, and G.A. Kalabin, *Tetrahedron Lett.*,1982, **23**, 5066.

30. A.M. Vasil'tsov, A.I. Mikhaleva, R.N. Nesterenko, and M.V. Sigalov, *Khim. Geterotsikl. Soedin.*, 1992, 477.

31. I.A. Aliev, S.E. Korostova, A.I. Mikhaleva, S.G. Shevchenko, S.N. Zeinalova, L.N. Sobenina, M.V. Sigalov, and B.P. Gasanov, *Khim. Geterotsikl. Soedin.*, 1991, 1320.

32. S.E. Korostova, S.G. Shevchenko, E.Yu. Shmidt, I.A. Aliev, I.M. Lazarev, and M.V. Sigalov, *Khim. Geterotsikl. Soedin.*, 1992, 609.

33. S.E. Korostova, S.G. Shevchenko, and M.V. Sigalov, *Khim. Geterotsikl. Soedin.*, 1991, 187.

34. I.A. Aliev, B.R. Gasanov, N.I. Golovanova, and A.I. Mikhaleva, *Khim. Geterotsikl. Soedin.*, 1987, 1486 (*Chem. Abstr.*, 1988, **109**, 22790).

35. S.E. Korostova, A.I. Mikhaleva, S.G. Shevchenko, M.V. Sigalov, and V. Yu. Vitkovsky, *Sulfur Lett.*, 1986, **5**, 39.

36. B.A. Trofimov, S.E. Korostova, L.N. Balabanova, and A.I. Mikhaleva, *Khim. Geterotsikl. Soedin.*, 1978, 489 (*Chem. Abstr.*, 1979, **90**, 71976).

37. S.E. Korostova, S.G. Shevchenko, M.V. Sigalov, and N.I. Golovanova, *Khim. Geterotsikl. Soedin.*, 1991, 460.

38. M.A. Yurovskaya, V.V. Druzhinina, E.V. Snetkova, and Yu.G. Bundel', *Khim. Geterotsikl. Soedin.*, 1983, 356 (*Chem. Abstr.*, 1983, **99**, 5475).

39. M.A. Yurovskaya, V.V. Druzhinina, and Yu.G. Bundel', III Vsesoyuznaya Konferentsiya po Khimii Geterotsikl. Soedin., Tezisi Dokladov, Rostov on Don, 1983, p. 83.

40. V.V. Druzhinina, thesis for Candidate of Chemical Sciences, Moscow, 1983.

41. M.A. Yurovskaya, V.V. Druzhinina, M.A.Tyurekhodzhaeva, and Yu.G. Bundel', *Khim. Geterotsikl. Soedin.*, 1984, 69 (*Chem. Abstr.*, 1984, **100**, 693).

42. M.A. Tyurekhodzhaeva, III Vsesoyuznaya Konferentsiya po Khimii Reaktivov, Tezisi Dokladov, Vol. 1, Ashkhabad, 1989, p. 93.

43. A.I. Mikhaleva, R.N.Nesterenko, A.M. Vasil'tsov, G.A. Kalabin, and N.I. Golovanova, *Khim. Geterotsikl. Soedin.*, 1992, 708.

44. B.A. Trofimov, A.I. Mikhaleva, A.N. Vasil'ev, V.A. Lopyrev, I.A. Titova, V.M. Bzhezovsky, and M.V. Sigalov, *Khim. Geterotsikl.Soedin.*, 1981, 1422 (*Chem. Abstr.*, 1982, **96**, 199581).

45. Jpn. Pat. 33890 (1970); *Ref. Zh. Khim.* 18H363 (1971).

46. L.V. Sokolyanskaya, A.N. Volkov, and B.A. Trofimov, *Zh. Org. Khim.*, 1976, **12**, 905 (*Chem. Abstr.*, 1976, **85**, 20663).

47. B.A. Trofimov, L.V. Sokolyanskaya, A.N. Volkov, A.I. Mikhaleva, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 1980, 2803 (*Chem. Abstr.*, 1981, **95**, 6401).

48. B.A. Trofimov, A.I. Mikhaleva, S.E. Korostova, and G.A. Kalabin, *Khim. Geterotsikl. Soedin.*, 1977, 994 (*Chem. Abstr.*, 1977, **87**, 151933).

49. M.A. Yurovskaya, A.Z. Afanas'ev, and Yu.G. Bundel', *Khim. Geterotsikl. Soedin.*, 1984, 1077 (*Chem. Abstr.*, 1984, **101**, 210914).

50. S.E. Korostova, A.I. Mikhaleva, B.A. Trofimov, S.G. Shevchenko, and M.V. Sigalov, *Khim. Geterotsikl. Soedin.*, 1992, 485.

51. L.N. Sobenina, S.E. Korostova, M.V. Sigalov, and N.N. Kalinina, VII

Vsesoyuznaya Konferentsiya po Khimii Atsetilena, Tezisi Dokladov, Erevan, 1984, p. 96.

52. L.N. Sobenina, A.I. Mikhaleva, S.E. Korostova, and M.V. Sigalov, *Zh. Org. Khim.*, 1990, **26**, 53.

53. B.A. Trofimov, A.I. Mikhaleva, R.N. Nesterenko, G.A. Kalabin, and O.A. Tarasova, *Zh. Org. Khim.*, 1988, **24**, 2626 (*Chem. Abstr.*, 1988, **111**, 96760).

54. A.M. Vasil'tsov, A.I. Mikhaleva, R.N. Nesterenko, and G.A. Kalabin, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 1989, 1702 (*Chem. Abstr.*, 1990, **112**, 98110).

55. B.A. Trofimov, S.G. Shevchenko, S.E. Korostova, A.I. Mikhaleva, and V.V. Scherbakov, *Khim. Geterotsikl. Soedin.*, 1985, 1573 (*Chem. Abstr.*, 1986, **105**, 78786).

56. S.E. Korostova, S.G. Shevchenko, and M.V. Sigalov, *Khim. Geterotsikl. Soedin.*, 1991, 1374.

57. B.A. Trofimov, S.G. Shevchenko, S.E. Korostova, A.I. Mikhaleva, M.V. Sigalov, and L.B. Krivdin, *Khim. Geterotsikl. Soedin.*, 1989, 1566 (*Chem. Abstr.*, 1990, **113**, 40497).

58. I.A. Aliev, A.I. Mikhaleva, B.P. Gasanov, and N.I. Golovanova, *Khim. Geterotsikl. Soedin.*, 1990, 1337.

59. A.I. Mikhaleva, B.A. Trofimov, A.N. Vasil'ev, G.A. Komarova, and V.I. Skorobogatova, *Khim. Geterotsikl. Soedin.*, 1982, 1202 (*Chem. Abstr.*, 1983, **98**, 16538).

60. S.E. Korostova, L.N. Sobenina, A.I. Mikhaleva, R.N. Nesterenko, S.G. Shevchenko, V.B. Modonov, and R.I. Polovnikova, *Zh. Org. Khim.*, 1988, **24**, 2538 (*Chem. Abstr.*, 1989, **111**, 38585).

61. I.A. Aliev, B.R. Gasanov, S.N. Zeinalova, and A.I. Mikhaleva, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 1988, 2175 (*Chem. Abstr.*, 1989, **110**, 154087).

62. S.E. Korostova, R.N. Nesterenko, A.I. Mikhaleva, R.I. Polovnikova, and N.I. Golovanova, *Khim. Geterotsikl. Soedin.*, 1989, 901 (*Chem. Abstr.*, 1990, **112**, 178530).

63. S.E. Korostova, A.I. Mikhaleva, S.G. Shevchenko, M.V. Sigalov, and I.N. Domnin, *Zh. Org. Khim.*, 1988, **24**, 1789 (*Chem. Abstr.*, 1989, **110**, 154086).

64. T.N. Borisova, A.E. Aliev, E.A. Sahnova, A.A. Sinitsina, and A.V. Varlamov, *Khim. Geterotsikl. Soedin.*, 1993, 137.

65. B.A. Trofimov, A.I. Mikhaleva, A.S. Atavin, and E.G. Chebotareva, *Khim. Geterotsikl. Soedin.*, 1975, 1427 (*Chem. Abstr.*, 1976, **84**, 59121).

66. A.E. Chichibabin, *Bull. Soc. Chim. France*, 1939, **6**, 522.

67. B.A. Trofimov, A.I. Mikhaleva, and A.N. Vasil'ev, *Zh. Org. Khim.*, 1976, **12**, 1180 (*Chem. Abstr.*, 1976,**85**, 93916).

68. S.E. Korostova, S.G. Shevchenko, M.V. Sigalov, and L.N. Sobenina, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 1990, 2659.

69. S.E. Korostova and S.G. Shevchenko, *Zh. Org. Khim.*, 1991, **27**, 2020.

70. H. Fischer and H. Orth, 'Die Chemie des Pyrroles,' Akademische Verlag, Leipzig, 1934.

71. S.E. Korostova and S.G. Shevchenko, *Khim. Geterotsikl. Soedin.*. 1990, 1695.

72. S. Ranganathan, D. Ranganathan, R.S. Sidhu, and A.K. Mehrotra, *Tetrahedron Lett.*, 1973, 3577.

73. A. Eckersley and N.A. Rogers, *Tetrahedron Lett.*, 1974, 1661.

74. H. Irei, I. Katayama, and Y. Mizuno, *Heterocycles*, 1979, **12**, 771.

75. A.I. Mikhaleva, O.V. Petrova, V.M. Bzhezovsky, and N.A. Kalinina, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 1987, 1677 (*Chem. Abstr.*, 1988, **108**, 221308).

76. B.A. Trofimov, A.I. Mikhaleva, and O.V. Petrova, *Zh. Org. Khim.*, 1991, **27**, 1941.

77. C. Gonzalez, R. Grenhouse, R. Tallabs, and Y.M. Muchowski, *Can. J. Chem.*, 1983, **61**, 1697.

78. B.A. Trofimov, S.E. Korostova, S.G. Shevchenko, E.A. Polubentsev, and A.I. Mikhaleva, *Zh. Org. Khim.*, 1990, **26**, 1110 (*Chem. Abstr.*, 1990, **113**, 151614).

79. B.A. Trofimov, A.B. Shapiro, R.N. Nesterenko, A.I. Mikhaleva, G.A. Kalabin, N.I. Golovanova, I.V. Yakovleva, and S.E. Korostova, *Khim. Geterotsikl. Soed.*, 1988, 350 (*Chem. Abstr.*, 1989, **110**, 38923).

80. B.A. Trofimov, S.E. Korostova, S.G. Shevchenko, and A.I. Mikhaleva, *Zh. Org. Khim.*, 1990, **26**, 940 (*Chem. Abstr.*, 1990, **113**, 151610).

81. B.A. Trofimov, T.I. Vakul'skaya, S.E. Korostova, S.G. Shevchenko, and A.I. Mikhaleva, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 1990, 142 (*Chem. Abstr.*, 1990, **112**, 215904).

82. T.I. Vakul'skaya, B.A. Trofimov, A.I. Mikhaleva, S.E. Korostova, S.G. Shevchenko, and L.N. Sobenina, *Khim. Geterotsikl. Soedin.*, 1992, 1056.

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