

REACTION OF KETOXIMES WITH ACETYLENE: A NEW GENERAL METHOD
FOR THE SYNTHESIS OF PYRROLES (REVIEW)

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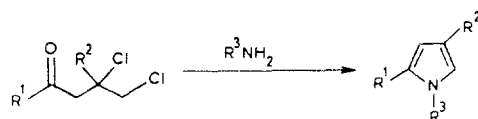
The results of the development of a new general synthesis of pyrroles based on the reaction of ketoximes with acetylene in superbase catalytic systems of the strong base-dimethyl sulfoxide (DMSO) type are analyzed thoroughly. The experimental conditions, the preparative possibilities, the probable mechanisms, and the prospects for the further development of the reaction are examined.

Interest in the chemistry of pyrroles has been increasing appreciably in recent years: Two fundamental monographs [1, 2] and a detailed review [3] have been published, and the flow of other publications is increasing [2]. This is being promoted to no small degree by the isolation of a large number of relatively simple pyrrole compounds, viz., antibiotics, pheromones, and toxins, from natural objects [1, 2, 4].

A number of simple pyrroles (primarily 2-acetylpyrrole) have been detected among the volatile components of black tea and Japanese hops and in tobacco leaves, valerian, and roasted coffee and cacao beans. Many plant alkaloids are pyrrole-2-carboxylic acid esters [1].

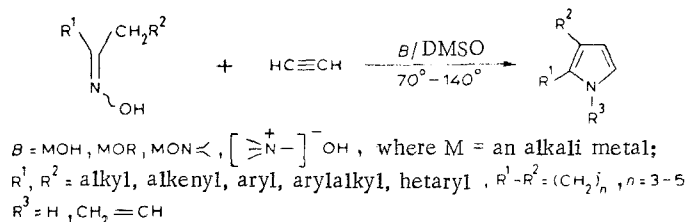
However, as Jones and Bean emphasized in their monograph [2], precisely the synthesis of simple pyrroles, particularly alkyl-substituted pyrroles, has always been fraught with great difficulty. Unfortunately, of the 39 reactions for the construction of a pyrrole ring presented by Gossauer [1], few have preparative value.

The small number of truly simple and general methods for the preparation of pyrrole systems were recently supplemented by new methods that have not yet been included in monographs and reviews. For example, one of them, which was developed by Kost, is the interesting heteroaromatization of β,γ -dichloropropyl ketones under the influence of ammonia and primary amines.



This method can be used to synthesize 2-, 1,2-, 2,4-, and 1,2,4-substituted pyrroles in 60-90% yields [5-7].

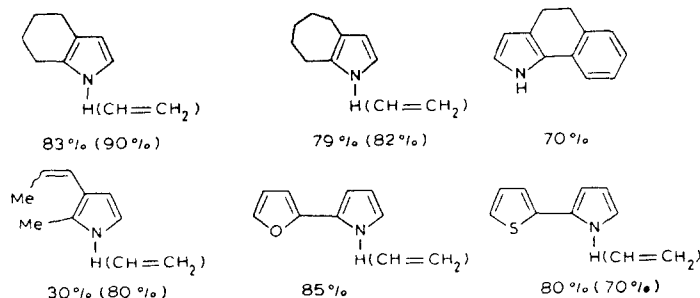
Another method that is perhaps undergoing the most intensive development at the present time is based on a new reaction involving the heterocyclization of ketoximes with acetylene, which we discovered in 1970 [8-10].



The results of the systematic development of this reaction are correlated briefly in the present review.

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As demonstrated in the scheme presented above, the reaction makes it possible to obtain the most diverse 2-, 2,3-, 2,5-, and 2,3,5-substituted pyrroles and (for the first time) their N-vinyl derivatives. The yields depend markedly on the structures of the starting reagents; however, in the case of simple ketoximes and unsubstituted acetylene they are quite steady and amount to 70-95% under optimal conditions [8-13, 16-18, 20, 21]. In addition to simple alkyl- and aryl-substituted pyrroles, those that were previously difficult to obtain by the usual methods or were not known at all, such as annellated pyrroles, obtained from the oximes of cyclohexanone [8-21], suberone [22, 23], tetralones [24], and decalones and substituted decalones, or various alkenyl-, furyl- [25, 26], and thienylpyrroles [27], as well as their vinyl derivatives [28, 29], have also become accessible.

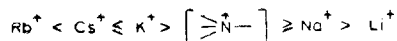


Reaction Conditions

Heterocyclization [8-26] proceeds smoothly at 70-140°C and most often [8, 9, 20, 21, 30, 31] at 90-100°C. Sometimes it is sufficient to simply heat the reagents up to this temperature until a mild exothermic process, the thermoregulation of which can subsequently be realized only by the inflow of acetylene, commences.

The synthesis is carried out extremely simply: Acetylene is passed into the heated and stirred solution of the reagents at atmospheric pressure [8, 20, 21, 30, 31]. An average of 3-5 h is required for completion of the reaction. An autoclave can, of course, also be used — the process goes to completion faster under pressure [8-12, 16-18, 20, 21].

The reaction is catalyzed specifically by a superbases pair [15-18], viz., a strong base-dimethyl sulfoxide (DMSO) system. An alkali metal hydroxide [8-13, 15-18, 20-22, 24, 25] is usually employed as the strong base, although oximates [8, 20, 21], alkoxides [8, 9, 20, 21], and quaternary ammonium bases are also active. A distinct dependence of the activity of the catalytic system on the nature of the cation is observed: In general, the activity increases as the volume of the cation increases, but the peak activity is observed for potassium:

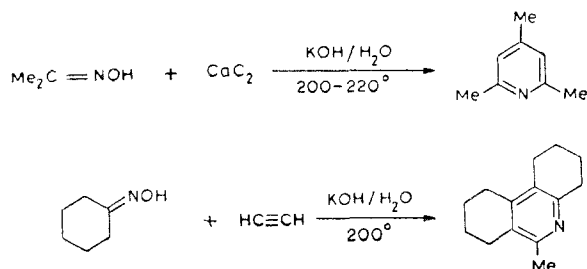


The sequence presented above is valid for many oximes of aliphatic and alicyclic ketones; however, it is not absolute and may evidently change as a function of the reaction conditions and the type of ketoxime. For example, tetrabutylammonium hydroxide, which quite actively catalyzes the synthesis of 4,5,6,7-tetrahydroindole from cyclohexanone oxime and acetylene [30], proved to be virtually inert in the case of alkyl aryl ketoximes [32].

The bases differ not only with respect to their activities but also with respect to their selectivities [30, 33, 34]. Thus, lithium hydroxide selectively catalyzes the heterocyclization of alkyl aryl ketoximes with acetylene [32-35] but is inactive in the step involving the vinylation of the resulting pyrroles. At the same time, LiOH is ineffective in both steps in the case of alicyclic ketoximes [33] — the construction of the pyrrole fragment in this case is accelerated selectively by rubidium and tetrabutylammonium hydroxides [30, 36]. The reaction rate increases as the base concentration in the reaction mixture increases [32]; good preparative results can also be obtained in the case of superstoichiometric excesses of the base with respect to the ketoxime (even excesses on the order of tenfold amounts). However, the optimal ratio of the ketoxime and the alkali is generally close to an equimolar amount [8, 9, 20, 21, 30-34].

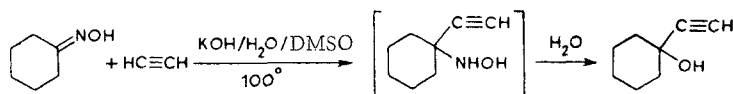
As compared with DMSO, its aprotic dipolar analogs, viz., hexametaol and sulfolane, form less active catalytic media [8, 9, 20, 21, 30-34], or, at least, the variants that involve their use have undergone less development and as yet do not have preparative value. The reaction does not occur at all in solvents such as dioxane, alcohols, and hydrocarbons.

In aqueous media, however, acetylene and ketoximes react in a completely different way, giving pyridines instead of pyrroles [37, 38]. Acetone oxime, for example, gives sym-collidine [37], while cyclohexanone oxime gives 6-methyl-1,2,3,4,7,8,9,10-octahydrophenanthridine. The reaction also takes place with acetylene obtained directly in the autoclave from calcium carbide [37].



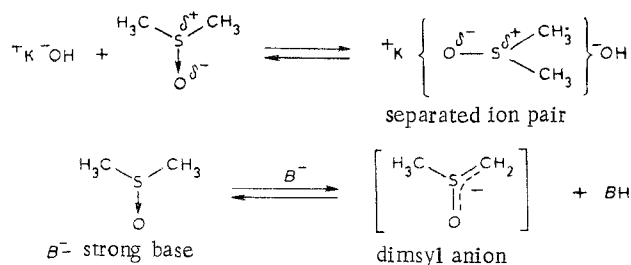
According to the results of preliminary experiments [37, 38] the yields of pyridines are low (~10% when CaC_2 is used [37] and 20-30% when pure acetylene is used); however, this reaction has not yet been investigated in greater detail.

Tertiary acetylenic alcohols (in up to 50% yields) are formed from ketoximes and acetylene in H_2O -DMSO (1:2 by volume) [39], i.e., we are dealing with a previously unknown analog of the Favorskii reaction here.

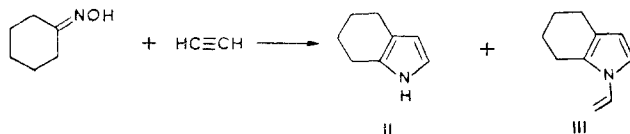


The reasons for such a critical effect of DMSO on the course of the reaction of ketoximes with acetylene evidently must be sought in the properties of "strong base-DMSO" systems that are classified as superbases [15-18, 40]. Their superhigh basicities are due in part to separation of the ion pair of the hydroxide due to strong specific solvation of the cation [41] and the formation of the highly basic and only slightly solvated dimsyl anion [40].

In such systems the basicity estimated from the acidity function is increased by many orders of magnitude [42, 43], the free energy of the anions increases sharply [44, 45], and the latter become supernucleophiles.



The catalytic function of DMSO is displayed particularly graphically when mixtures of it with dioxane are used in the heterocyclization of ketoximes with acetylene. The results for the following reaction are presented in Table 1 (dioxane, 20% KOH, 120°C, 2 h):



It is apparent from Table 1 that the reaction commences even in the case of a relatively small percentage of DMSO in the reaction mixture (5-10%). By varying the DMSO concentration one can actively affect the selectivity of the process and obtain either the NH-pyrrole (in the case of a small percentage of DMSO) or only the N-vinylpyrrole (in pure DMSO).

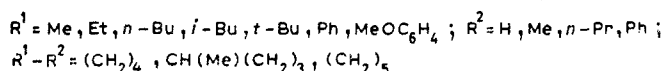
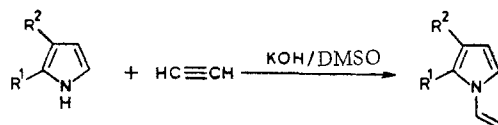
N-Vinylpyrroles

A study of the reaction of ketoximes with acetylene led to the development of a new efficient method for the vinylation of pyrroles [46-48], which is characterized by virtually

TABLE 1. Effect of the Composition of the Solvent on the Yields of the Products of the Reaction of Cyclohexanone Oxime with Acetylene

Amount of DMSO added to dioxane, parts by vol.	Overall yield (II + III), %		Percentage of N-vinyl derivative III in the mixture
	based on starting I	based on converted I	
0	0	0	0
0,05	10	30	0
0,14	35	67	0
0,32	40	82	10
1,5	53	87	80
Pure DMSO	77	93	99,5

quantitative (up to 97%) yields of N-vinyl derivatives and mild conditions (90–100°C at atmospheric pressure):

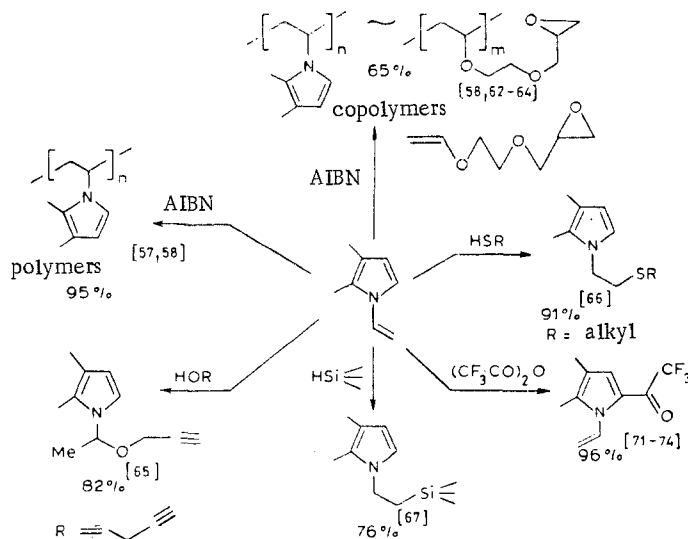


If one takes into account the fact that the direct vinylation of NH heterocycles until recently was accomplished at high temperatures (150–300°C) [49–53] and generally under an acetylene pressure of 20–40 atm [51–53], it is clear that we are therefore dealing with qualitative progress along the path of technologization of these important processes, the introduction of which has thus far been deterred precisely because of the necessity for the use of acetylene under pressure and at high temperatures.

Experimental batches of 4,5,6,7-tetrahydroindole and N-vinyl-4,5,6,7-tetrahydroindole are already being produced in pilot plants [47]. The latter compound has proved to be an effective repellent.

The possibility of the one-step synthesis of N-vinylpyrroles from ketoximes and acetylene is generally the fundamental feature of this reaction, especially since up to now N-vinylpyrroles have been virtually unknown. In addition to N-vinylpyrrole [1, 54, 55], only N-vinyl, N-propenyl, and N-(α -styryl) derivatives of pyrrole-2-carboxylic acid have been described [1, 56], whereas N-vinylpyrroles are promising monomers [47, 57, 58] and reagents for fine organic synthesis [47] (see Scheme 1). N-Vinylpyrroles undergo polymerization in the presence of certain quinones, carbon tetrachloride, boron trifluoride etherate [59], and azobisisobutyronitrile [47, 57, 58]. On the basis of quantum-chemical calculations it is assumed that N-vinylpyrroles are capable of polymerization also via an anionic mechanism [60, 61].

Scheme 1



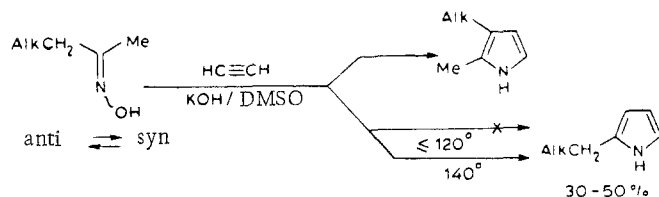
The polymers of N-vinylpyrroles are evidently capable of undergoing rearrangement to porphyrinlike structures by heat treatment in the presence of heavy metal ions. The copolymerization of N-vinylpyrroles with other monomers [62, 63] opens up new possibilities for the production of materials with a valuable set of properties [58, 62-64]. Co-oligomers of N-vinylpyrroles and vinyl epoxy ethers [58, 63, 64], which undergo hardening like ordinary epoxide resins and form structure-colored and photoconductive films with increased thermal stability [58, 64], are shown in the scheme.

N-Vinylpyrroles add various traditional addends, viz., alcohols [65], thiols [66], and hydrosilanes [67], smoothly. This makes them the forebears of large families of heretofore unknown N-(α - and β -hetero- and elementoethyl)-substituted pyrroles (Scheme 1). Methods for the selective [68] and exhaustive [69] hydrogenation of N-vinylpyrroles have been developed, and their complexes with bromine, iodine, and alkyl bromides, which are of the charge-transfer-complex (CTC) type, have been studied [70]. Selective electrophilic substitution in the pyrrole ring (for example, trifluoroacetylation [71-76]) can be carried out with retention of the N-vinyl group (Scheme 1); this increases the importance of N-vinylpyrroles as starting materials and monomers to an even greater extent.

Preparative Limitations and Structural Specificity of the Reaction

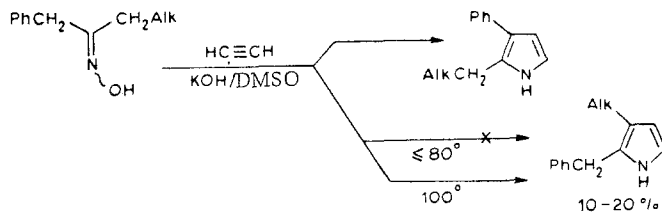
How wide is the scope of the preparative possibilities of the heterocyclization of ketoximes with acetylene? It is evidently still too early to give a definite answer to this question. In any case, virtually all ketoximes that contain at least one methylene or methyl group in the α position relative to the oxime function [8-27, 30-35, 77] and, naturally, do not contain substituents that are sensitive to the action of bases undergo the reaction.

In the case of unsymmetrical ketoximes in which competition between the methyl and methylene groups is possible, the pyrrole ring is constructed regiospecifically, i.e., only through the methylene group, at moderate temperatures (up to 120°C) [78]. However, at 140°C the relative percentage of a second isomeric pyrrole (constructed through the methyl group) in the mixture of products may reach 50% [78].



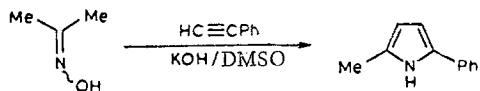
Since ketoximes exist primarily in the syn configuration [79, 80], it is clear that, like the Beckmann rearrangement [81], the reaction proceeds with the participation of the grouping in an anti orientation with respect to the hydroxy group. As the temperature is raised, under the reaction conditions the configurational equilibrium is evidently shifted to favor the anti isomer, as a consequence of which the regiospecificity of the reaction is disrupted.

If two different methylene groups compete for the construction of the pyrrole ring, as, for example, in ethylbenzylketoxime, the methylene group in an anti orientation relative to the hydroxy group, i.e., in this case the methylene group of the benzyl grouping wins. In this case also the virtually complete selectivity that is observed at temperatures below 80°C is disrupted as the temperature is raised.



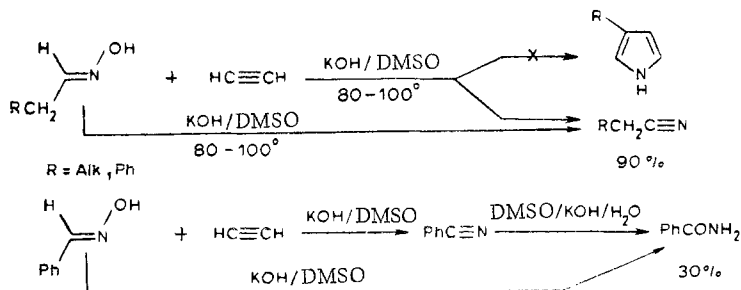
Some substituted acetylenes (for example, phenylacetylene [16-18, 82]) that are not capable for undergoing prototropic isomerization and are stable in the presence of strong bases also undergo the reaction with ketoximes. In this case also heterocyclization proceeds regiospecifically: The phenyl group enters exclusively the α position of the pyrrole ring,

but the outcome of the reaction is independent of the temperature.

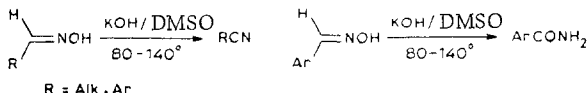


Ketoximes that contain tertiary or aromatic groupings in any combinations do not form pyrroles [17]. In the case of ketoximes with secondary alkyl groupings one might expect the formation of pyrrolenines (3H-pyrroles); however, this possibility has not yet been realized.

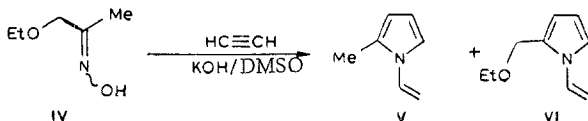
Under the conditions of the reaction under consideration aliphatic aldoximes are converted nitriles in high yields [12, 18, 38, 83], while aromatic aldoximes are converted to both nitriles and amides [83]; the latter are not formed via the scheme of the first-order Beckmann rearrangement but rather through the intermediate nitrile (this was proved by the isolation of benzonitrile and its subsequent hydration to give benzamide under the same conditions) [83].



Thus, instead of a synthesis of 2-unsubstituted pyrroles, a new method for the dehydration of aldoximes to nitriles and, evidently, the first alkaline variant of the Beckmann rearrangement were found [83].

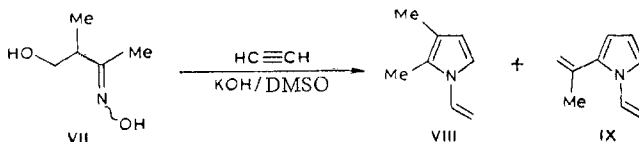


Oximes of α - and β -hydroxy ketones react with acetylene (80-110°C, KOH and DMSO) to give primarily mixtures of pyrroles that do not contain oxygen-containing functions in low yields (~20%) [84, 85]. The simplest member of the series, viz., 1-hydroxy-2-propanone oxime, is unstable under the usual conditions of the reaction of ketoximes with acetylene and undergoes complete resinification. Its ethyl ether (IV) is more stable and upon reaction with excess acetylene is converted to an anomalous product, viz., 1-vinyl-2-methylpyrrole (V), in up to 15% yield, which often exceeds the yield of the expected 1-vinyl-2-ethoxymethylpyrrole (VI) [85]. It is interesting that, in contrast to methyl n-alkyl

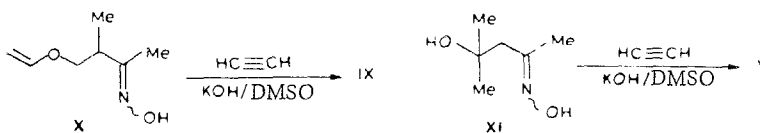


ketoximes, which form a pyrrole ring primarily through the methylene group of the n-alkyl grouping, 1-ethoxy-2-propanone oxime furnishes only a methyl group for this.

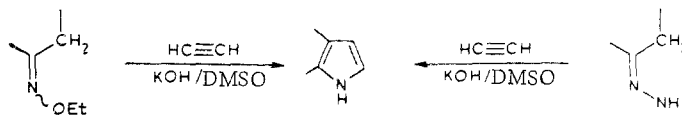
2-Methyl-1-hydroxy-3-butanone oxime (VII) reacts with excess acetylene in an autoclave at 100°C to give two anomalous reaction products, viz., 1-vinyl-2,3-dimethylpyrrole (VIII) [84, 85] and 1-vinyl-2-isopropenylpyrrole (IX) in 20 and 8% yields, respectively.



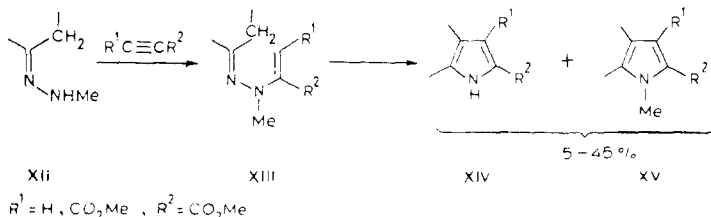
The vinyl ether (X) of oxime VIII also reacts with excess acetylene to give pyrrole IX; however, pyrrole VIII is not formed in this case. 2-Methyl-2-hydroxy-4-pentanone oxime (XI) reacts with acetylene to give 1-vinyl-2-methylpyrrole (V) in ~20% yield [85].



We have not yet been able to obtain pyrroles by condensation of acetylene with the O-ethyl ethers of ketoximes and hydrazones, i.e., we have not been able to realize possible analogs of the reaction under investigation:

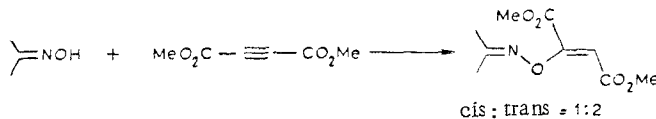


However, Baumes and co-workers [86] later had considerable success in this direction using methylhydrazones (XII) and, instead of acetylene, methyl esters of propiolic and acetylenedicarboxylic acids. The obtained mixtures of the corresponding 4- and 4,5-methoxycarbonylpyrroles (XIV) and their N-methyl derivatives XV in 5-45% yields. The reaction proceeds through the intermediate N-vinylhydrazones XIII. In addition, this once again demonstrates the fundamental differences in the reactivities of unsubstituted acetylene, on the one hand, and acetylenes with especially strong acceptor substituents (the so-called activated acetylenes), on the other.

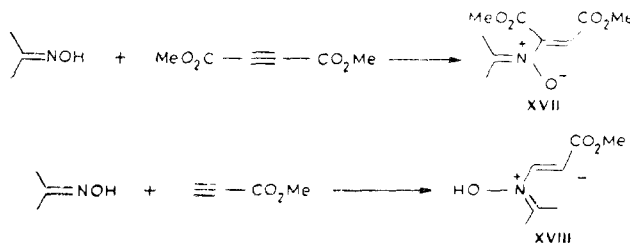


Reaction Mechanism

In our discussion of the reaction mechanism we must note that the results of previous studies of the reaction of oximes with acetylenes are in poor agreement. Thus, according to the data in [87], ketoximes add to dimethyl acetylenedicarboxylate by means of their hydroxy group to give O-vinyl derivatives XVI.



However, it follows from [88-94] that such reactions lead to N-vinylnitrones XVII [88-90, 94] or N-vinyl zwitterion intermediates XVIII [91, 92, 94], which subsequently add a second molecule of acetylene to give oxazole [88-91, 92] or pyridine [93] derivatives.



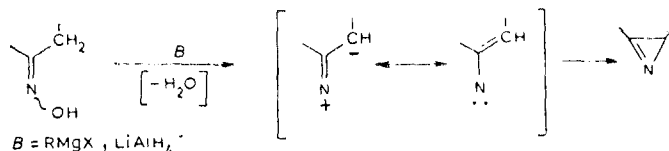
A report [95] of the direct vinylation of acetoxime was not confirmed when it was checked [96].

It is known that ketoximes in a number of cases behave like C-H acids: For example, they undergo metallation at the methyl or methylene group [97-100]. The possibility that it is precisely the C-H acidity of the ketoximes that is of primary importance in the KOH-DMSO superbase system cannot be excluded. The deuterium exchange between DMSO and the α -methyl groups of ketoximes that we observed [13] under the reaction conditions may serve as

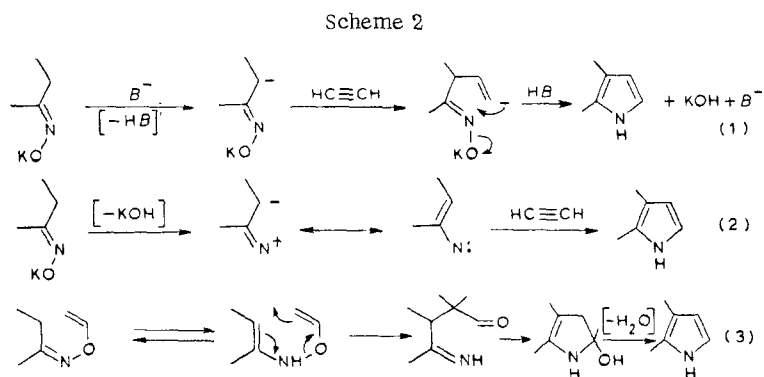
a configuration of this. In any case, the tridentate character of the oximate anion, i.e., its ability to act as an O-, N-, and C-nucleophile, very much complicates the analysis of the mechanism of the base-catalyzed heterocyclization of ketoximes with acetylene.



One also cannot disregard the possibility of the participation of an aziridine intermediate [12-14, 16-18, 38] or its open forms, viz., a 1,3-dipole [12-14, 16-18, 38] or a vinylnitrene [16-18], in the reaction, for the ability of ketoximes to undergo 1,3-dehydration with the formation of azirines (the Hoch-Campbell reaction) under the influence of strong bases is known [101-112].

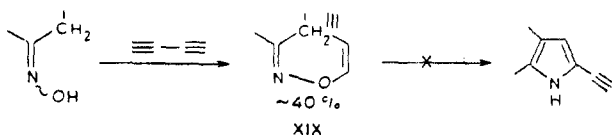


In light of these data we can discuss the following heterocyclization mechanisms (Scheme 2): 1) nucleophilic attack on acetylene by the anionic part of the ketoxime (only the key steps are shown in the scheme); 2) 1,3-dehydration of the ketoxime and addition of the 1,3-dipole (or the vinylnitrene corresponding to it) to the triple bond; 3) [3,3]-sigmatropic shift in the intermediate O-vinyl oximes.

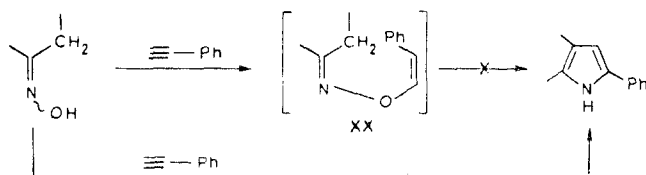


The latter mechanism is still in contradiction with most of the available facts. The lower O-vinyl oximes isolated in low yields (~5%) from the reaction products [16, 18, 113] do not give pyrroles upon thermolysis in the absence of acetylene. However, a brief note to the effect that more complex O-vinyl oximes that contain carboxylate functions in the α and β positions of the vinyl group undergo decomposition at 180°C to give pyrroles has been published [87].

The expected ethynylpyrroles also cannot be obtained by using diacetylene, but the corresponding cis-O-(β -ethynylvinyl) oximes XIX are formed quite readily in this case [114, 115].

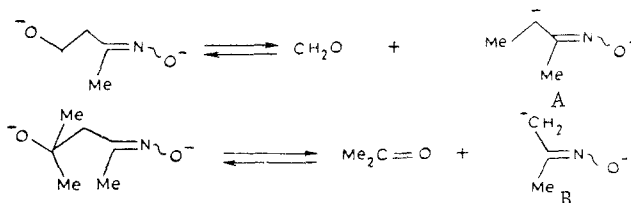


The structural specificity of heterocyclization examined above is also not in agreement with the O-vinyl oxime pathway: If the vinyl oxime undergoes rearrangement, the pyrrole ring should evidently be constructed primarily through the syn- α -methyl group, whereas only the anti- α -methylene fragment is actually regiospecifically involved in the cyclization at the optimal temperature. As we demonstrated above, however, α - rather than β -phenyl-substituted pyrroles are formed with phenylacetylene; this could not be true in the case of rearrangement of the corresponding cis-O-(β -phenyl) oximes (XX), which, according to the known principles of nucleophilic addition to a triple bond [116], should have precisely this structure.

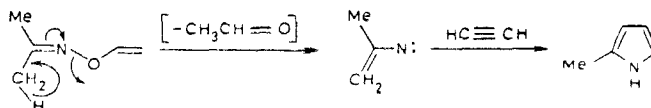


At the same time, the results obtained [84, 85] with respect to the reaction of oximes of α - and β -hydroxy ketones with acetylene discussed in the preceding section may constitute evidence in favor of the important role of the carbanions in the first steps of the construction of a pyrrole ring. The observed regiospecificity of the reaction of 1-ethoxy-2-propanone oxime with acetylene [85] can be explained precisely from this position.

The formation of 2-methyl- and 2,3-dimethylpyrroles (V and VIII) from 2-methyl-1-hydroxy-3-butanone oxime (VII) and 2-methyl-2-hydroxy-4-pentanone oxime (XI) described above may be due to dissociation of these oximes in the form of dianions via a scheme that resembles reversible aldol condensation [85].



Carbanions A and B upon subsequent reaction with acetylene can be converted, respectively, to pyrroles V and VIII via reaction (1) (Scheme 2). In addition, according to preparative data [17, 18], it was possible [by gas-liquid chromatography (GLC)] to establish the formation of the corresponding pyrroles in the decomposition of O-vinyl oximes in the KOH-DMSO superoxide system in the presence of acetylene; this can be interpreted as evidence in favor of a vinylnitrene mechanism:



Nevertheless, the experimental data available are still not sufficient to make a definite choice among the mechanisms examined above (Scheme 2). Moreover, one cannot lose sight of the fact that even the most verisimilar schemes cannot be considered to be adequate if they do not explain why heterocyclization proceeds successfully only in the presence of the specific strong base-DMSO superbases system.

The systematic study of the new synthesis of pyrroles from ketoximes and acetylene is continuing. It may be hoped that this will lead not only to further expansion of the preparative possibilities of the reaction but also to the discovery of new variants and analogs. The increased accessibility of pyrroles is already stimulating synthetic [117] and theoretical [118, 119] studies in this area. In any case, the reaction of ketoximes with acetylene is already at that stage of its development in which it can be recommended as a reliable preparative instrument for mass application in the chemistry of pyrrole.

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ELECTRONIC ABSORPTION SPECTRA AND ACIDITIES OF HETEROAROMATIC

THIOLS

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The electronic absorption spectra of a number of substituted and unsubstituted thiophene-, benzothiophene-, and benzofuranthiols were studied, and their ionization constants were determined by establishment of the dependence of the optical densities of aqueous alcohol solutions of them on the pH.

A number of papers [1-3] have been devoted to the study of the acidities of phenols, thiophenols, and quinolinethiols by titrimetric and spectrophotometric methods and the effect of structural factors on the acidities. However, systematic studies of a similar sort for heteroaromatic thiols that contain furan and thiophene structural fragments are not available in the literature.

In the present research we obtained the pK_a values of a number of substituted and unsubstituted thiophene-, benzothiophene-, and benzofuranthiols by determination of the dependence of the optical densities of aqueous alcohol solutions of the thiols on the pH. A preliminary analysis of the UV spectra of heteroaromatic thiols showed that these compounds exist exclusively in the thiol form (the UV spectra of thiols I-XI do not contain the absorption band of a C=S group at 490-510 nm) (Table 1). The introduction of electron-donor substituents in the thiol molecules generally gives rise to a bathochromic shift in the electronic absorption spectra (218 \rightarrow 232 nm for VII and VIII, and 218 \rightarrow 233 nm for VII and IX). Replacement of a hydrogen atom in the thiophene ring by an electron-acceptor chlorine atom leads to a hypsochromic shift of the maximum of the absorption band of the mercapto group (219 \rightarrow 206 nm for I and VI). Greater changes in the electronic absorption spectra occur when electron-donor substituents are introduced in the benzothiophene molecule than in the case of benzofuran (VII, VIII, and IX; X and XI); this is associated with the lower degree of aromatic character of the latter.

A comparison of the pK_a values of benzofuran-2-thiols and the corresponding benzothiophene-2-thiols shows that replacement of the sulfur atom in the heteroring by the more electronegative oxygen atom gives rise to weakening of the S-H bond and, as a consequence, an increase in the acidity of the corresponding thiol (Table 1). A similar effect is observed when the hydrogen atom in the 5 position of thiophene-2-thiol (I) is replaced by a chlorine atom (VI); in this case the acidity of the thiol increases by almost an order of magnitude. A similar effect of electron-acceptor substituents on the pK_a values was noted for substituted thiophenols [2] and phenols [1]. The introduction of electron-donor substituents in thiol molecules promotes strengthening of the S-H bond, and the acidity of the thiol decreases in this case (III, IV, V, VIII, IX, and XI). Annellation of the thiophene ring with a benzene

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