APPLICATION OF THE SCHMIDT REACTION FOR THE PREPARATION OF TETRAZOLES (REVIEW)

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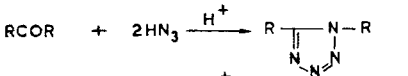
The application of the Schmidt reaction with ketones and nitriles for the preparation of tetrazoles is examined. Modern concepts regarding the mechanism of the reaction of ketones and nitriles with hydrazoic acids are discussed. The range of application of the reaction is indicated.

Tetrazoles are finding ever-increasing application in medicine [1-4], the chemistry of azo dyes [5], photography [6], the manufacture of plastics [7, 8], agriculture [9, 10], etc. The properties of tetrazoles and methods for their preparation have been examined in reviews [11, 12]. However, of the numerous methods for the synthesis of these compounds only a small amount of space has been allotted to the Schmidt reaction with ketones and nitriles. In most cases this reaction is used for the preparation of substituted amides, and the formation of tetrazoles is considered to be a side process [13]. At the same time, the Schmidt reaction can be recommended as a universal method for the synthesis of substituted tetrazoles, inasmuch as the preparation of compounds of this type by other methods is sometimes impossible. A characteristic feature of the Schmidt reaction is the addition of hydrazoic acid to an iminocarbonium ion formed as an intermediate particle. For this reason, some of the principles characteristic for this reaction can be extended to processes such as the addition of hydrazoic acid to imidochlorides and nitriles. Modern concepts regarding the mechanism of the reaction of ketones and nitriles with hydrazoic acid are set forth from these positions in the present review, and the range of application of this reaction is indicated.

Preparation of 1,5-Disubstituted Tetrazoles from Ketones

General Characteristics of the Reaction. The formation of tetrazoles from ketones and hydrazoic acid in the presence of acid catalyst was first observed by Schmidt in 1924 [14]. Depending on the ratio of the starting reagents, 1,5-disubstituted tetrazoles or aminotetrazoles may be obtained:



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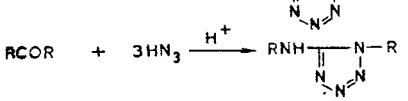

(2)

It was subsequently shown that this reaction is a general reaction for ketones with various structures — from the simplest ketones to compounds having complex structures, for example, triterpenoids [15]. However, the formation of an aminotetrazole was observed in only one case — in the reaction of benzophenone with excess hydrazoic acid [14]. It should be noted that substituted amides are formed along with tetrazoles from ketones. The tetrazole to amide ratio depends on the structure of the ketones, the nature of the catalyst used, and the reaction conditions.

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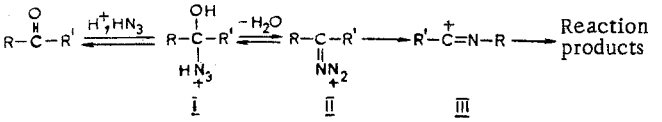
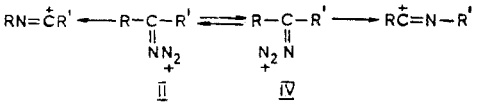
In earlier studies devoted to the reaction of ketones with hydrazoic acid no reasons for the formation of tetrazoles are presented, although Schmidt erroneously assumed that the rearrangement occurs as a result of reaction of the ketones with an imine radical (NH) formed during cleavage of the hydrazoic acid. The fundamentals of the modern concepts regarding the mechanism of the Schmidt reaction were formulated by Smith [16, 17]. Smith substantiated the formation of tetrazoles from ketones and hydrazoic acid in conformity with these concepts.

Mechanism of the Reaction of Ketones with Hydrazoic Acid. The mechanism of the reaction of ketones with hydrazoic acid has been studied in detail [18-22] and can be represented as follows:



(3)

The first step is addition of unprotonated hydrazoic acid to the protonated ketone, and the resulting azidohydrin (I) undergoes dehydration to give an iminodiazonium ion, which can exist in the form of syn (II) and anti (IV) conformers:

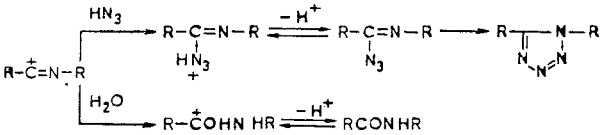


(4)

The assumption of the existence of equilibrium (4) makes it possible to explain the formation of isomeric tetrazoles and amides from unsymmetrical ketones.

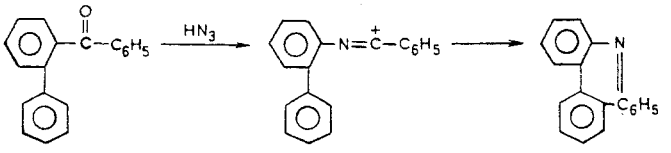
Elimination of nitrogen from the iminodiazonium ion is accompanied by migration of the substituent (R or R') in the anti position with respect to the diazo group. The iminocarbonium ion (III) formed as a result of rearrangement reacts with hydrazoic acid or another mucleophilic reagent to give the reaction products. Inasmuch as the Schmidt reaction with ketones is carried out in sulfuric acid in most cases, substituted amides are formed simultaneously with tetrazoles even when a considerable excess of hydrazoic acid is present.

Formation of Tetrazoles. According to [3], the formation of tetrazoles and substituted amides occurs as a result of two competitive reactions — reactions of hydrazoic acid and water with the iminocarbonium ion:

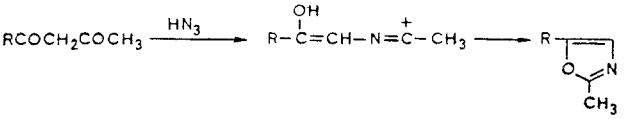


(5)

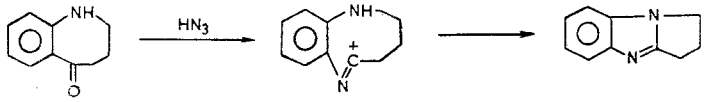
Arcus and co-workers [23] have expressed doubt about the validity of this mechanism, but there is now a great amount of evidence for the existence of the iminocarbonium ion as an intermediate particle in the reaction of ketones with hydrazoic acid. Thus 9-phenylphenanthridine is formed in the reaction of o-phenylbenzophenone with hydrazoic acid [24]:



Acetylacetone and benzylacetone undergo similar transformations [25]:

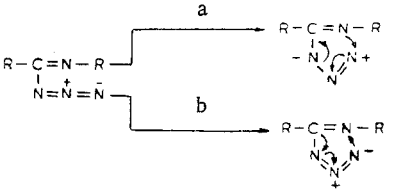


Some heterocyclic ketones give the corresponding benzimidazoles under the conditions of the Schmidt reaction [26].



The formation of "anomalous" products of the Schmidt reaction in all of the enumerated cases is the result of intramolecular attack of the iminocarbonium ion on the adjacent nucleophilic centers. Direct proof for the formation of the iminocarbonium ion was obtained in a study of the reaction of 2-hexanone with hydrazoic acid [27]. When the reaction is carried out in 80% H_2SO_4 containing H_2O^{18}, N-butylacetamide containing O^{18} is formed. When the reaction was carried out in 100% H_2SO_4 with subsequent dilution of the reaction mixture with H_2O^{18}, the N-butylacetamide did not contain O^{18}. Inasmuch as the oxygen atom of the ketone and the amide does not undergo exchange with the O^{18} of the medium under the reaction conditions, it follows from these results that the amide is formed during the reaction of the iminocarbonium ion with water, during which hydration is realized in the reaction medium and not after completion of the reaction when water is added, as was previously assumed [23].

According to [17], the formation of the tetrazoles occurs as a result of reaction of the iminocarbonium ions with hydrazoic acid and subsequent cyclization of the protonated imidazide. However, in later studies [28, 29] it was shown that the protonated imidazide, because of an appreciable decrease in the nucleophilicity of the imide nitrogen atom, is incapable of subsequent transformations. At the same time, imidazides in the form of the free bases with electron-donor substituents attached to the nitrogen and carbon atoms are stabilized by cyclization to isomeric tetrazoles [30, 31]. This is confirmed by the UV spectra of N-phenylacetamidazide in aqueous sulfuric acid solutions. Intense absorption at 290-292 nm, which is related to the protonated form of the imidazide [32], is observed in the UV spectrum of the imidazide in 90% sulfuric acid. However, a rapid decrease in the optical density in the indicated region is observed when the sulfuric acid concentration decreases to 25-30%. The latter fact is associated with deprotonation of the imidazide and conversion of it to the tetrazole. Similar results were obtained in a study of the cyclization of N-methylacetimidazide to 1,5-dimethyltetrazole [33]. The cyclization of imidazides to tetrazoles is the result of a cyclic electron transfer, during which two directions in which this reaction may proceed are possible:



(6)

The fundamental possibility of cyclization of the imidazide via path a is indicated in [34]. At the same time, it is assumed that the reaction of organic azides with nitriles proceeds via scheme b [35]. The cyclization of vinyl azides can probably be realized via either of these paths [36, 37]. Thus, one cannot predict the mechanism of cyclization of imidazides to tetrazoles on the basis of general considerations. Important results that make it possible to explain the mechanism of cyclization of imidazides were obtained in a study of the kinetics of cyclization of a series of N-arylacetimidazides in aqueous sulfuric acid solutions [28, 29]. The kinetic scheme of the cyclization of imidazides to tetrazoles can be written

$$BH^+ \overset{K_a}{\rightleftharpoons} B \overset{k}{\rightarrow} T \rightleftharpoons TH^+, \tag{7}$$

where BH^+ and B are the protonated and unprotonated imidazide, T and TH^+ are the unprotonated and protonated tetrazole, K_a is the protolytic equilibrium constant, and k is the cyclization rate constant. In this case the observed rate constant is related to the acidity of the medium by the expression [38]

$$k_{eff} = \frac{K_a \cdot k}{K_a + h_0}, \tag{8}$$

or

$$\frac{1}{k_{eff}} = \frac{1}{k} + \frac{1}{k \cdot K_a} h_0. \tag{9}$$

Under boundary conditions, when $h_0 >> K_a$ and $h_0 << K_a$, Eq. (8) takes on the form

$$k_{eff} = \frac{K_a \cdot k}{h_0} \quad (10)$$

or

$$\lg k_{eff} = \lg k \cdot K_a + mH_0 \quad (11)$$

$$\text{and } k_{eff} = k. \quad (12)$$

In the case of a series of substituted N-phenylacetimidazides it has been shown [29] that over a definite interval of acidities of the medium (when $h_0 >> K_a$), according to Eq. (11), a linear dependence of log k_{eff} on h_0 with a slope close to unity is observed (Fig. 1). It follows from this that all of the investigated imidazides are Hammett bases. The deviation from linearity in sulfuric acid at concentrations less than 35% for compounds 1, 2, and 3 (Fig. 1) is explained by the considerable increase in the fraction of the unprotonated form of the imidazide.* Over this range the k_{eff} value tends toward a limiting value equal to the true rate constant (k) [Eq. (12)].

The pK_a values (−0.70, −0.67, and −0.85, respectively) and k values (0.40, 0.54, and 0.75, respectively) were determined from the effective rate constants for cyclization in 0.1-30% H_2SO_4 by means of Eq. (9) for compounds 1, 2, and 3. Equation (9) can also be used for the determination of the pK_a and k values for the remaining imidazides, but because of the long-range extrapolation, the accuracy in the determination of the constants cannot be considered to be satisfactory. A dependence on the σ^- values is observed for the basicity constants and true cyclization reaction constants (Fig. 2). The relatively small change in the σ^- values for substituents such as H, CH_3, and CH_3O requires careful evaluation of the absolute ρ_{K_a} and ρ_k values, but there is no doubt about the increase in the true cyclization rate constants and the decrease in the basicities of the imidazides as the electronegativities of the substituents increase. It is interesting that there is a correlation between log $k \cdot K_a$ and the σ^- values for the investigated imidazides (Fig. 2).† The high correlation coefficient of this dependence over a broad range of change in the σ^- values constitutes evidence that the cyclization mechanism is the same for all of the investigated imidazides. In addition, on the basis of this it can be assumed that the true cyclization rate constants and the basicity constants of the imidazides correlate with one and the same σ^- substituent constants.

Valuable information obtained in a study of the kinetics of the cyclization of N-phenylacetimidazides and the results of correlation analysis make an appreciable contribution to an understanding of the mechanism of the formation of tetrazoles from ketones and hydrazoic acid. However, this is still not sufficient information for the formation of a judgment regarding the direction of electron transfer during the cyclization of imidazides to tetrazoles. The character of the electron transfer can apparently be ascertained by comparison of the basicities of the imides and terminal nitrogen atoms of the imidazide. The imide nitrogen atom in the imidazides is approximately in the sp^2 hybridized state, as in the case of Schiff bases or pyridines [39, 40]. It may be supposed that if protonation of the imidazides proceeds at the imide nitrogen atom, the basicity constants of these compounds would be close to the basicity constants of pyridines having an azide group or a group with similar electronic properties in the α position (the pK_a values of α-nitro-, α-fluoro-, and α-cyanopyridine are, respectively, −2.06, −0.44, and −0.26 [41, 42]). In fact, the basicity constants of imidizides range from −0.7 to −1.5 H units [29]. If imidazides were protonated at the azide group, one should have expected much lower pK_a values for these compounds. Thus, for example, the pK_a value of hydrazoic acid is −7.19 [43]. In addition, the leading nitrogen atom of the azide group should be the site of addition of a proton in imidazides in this case. This conclusion follows from the results of a calculation of the electronic strucute of hydrazoic acid and the reactivities of organic azides, in which the leading nitrogen atom is nucleophilic, and the terminal nitrogen is electrophilic [45]. At the same time, it is well-known that when imidazides are protonated at the leading nitrogen atom they are rearranged to give ureas [46]. However, substituted N-phenylacetimidazides are distinguished by their high stabilities in concentrated

*Because of the high rates of cyclization, the kinetics of the reaction for the other imidazides over this acidity range were not investigated.

†The log $k \cdot K_a$ values were taken from linear regression equations in accordance with expression (11) for constant H_0.

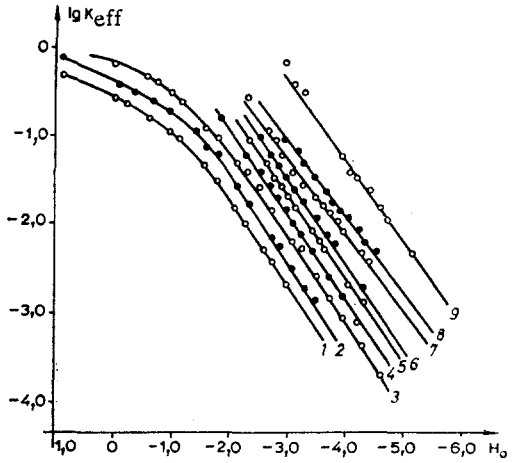


Fig. 1

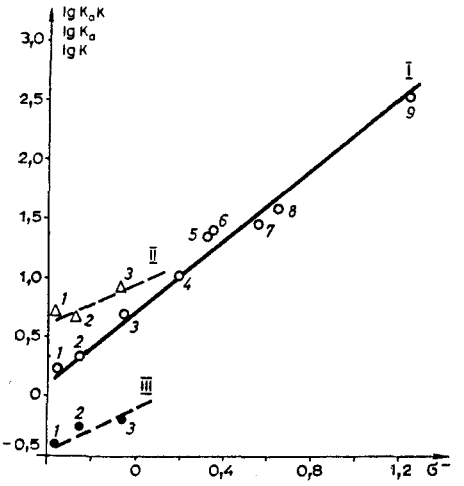


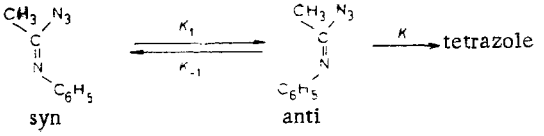
Fig. 2

Fig. 1. Dependence of log k_{eff} for cyclization of N-arylacetimidazides $RC_6H_4N = C(N_3)CH_3$ on acidity function H_0: 1) R = p-OCH_3; 2) R = p-CH_3; 3) R = H; 4) R = p-Cl; 5) R = m-Cl; 6) R = m-Br; 7) R = m-NH_2; 8) R = m-NO_2; 9) R = p-NO_2.

Fig. 2. Correlation dependence of log $k \cdot K_\alpha$ for the cyclization of N-phenylacetimidazides (I), log K_α (II), and log k (III) on the σ^- values (see Fig. 1 for the numbering of these compounds).

sulfuric acid [28]. Thus one should suppose that the imide nitrogen atom is the site of addition of a proton in imidazides. Under the assumption that the nucleophilicity of the nitrogen atom is determined by its basicity it may be supposed that the imide nitrogen atom in imidazides is nucleophilic, and that the terminal nitrogen atom is an electrophilic reaction center. Thus the formation of tetrazoles from imidazides occurs as a result of cyclic electron transfer via path a (scheme 6).

In order to present a complete picture one must also point out yet another peculiarity of the cyclization of imidazides; imidazides may exist in the form syn and anit conformers:



(13)

Tetrazoles are formed during the cyclization of the anti form. Analysis of geometrical models of imidazides shows that the phenyl ring is conjugated with the π electrons of the imide nitrogen atom only in the syn conformation. The phenyl ring is removed from conjugation in the anti conformation as a result of steric interaction with the methyl group. A comparison of the UV spectra of protonated Schiff bases [39, 40] and protonated imidazides attest to the fact that the phenyl ring is in conjugation with the π electrons of the imide nitrogen atom. It is very important that this sort of conjugation is also observed in unprotonated imidazides [28, 29]. Thus, regardless of the form in which the imidazide exists, the phenyl ring is conjugated with the π electrons of the imidazide system. As we have already shown, this sort of conjugation is observed only in the syn conformation, and equilibrium (13) is consequently shifted to favor the syn form. It follows from this that, depending on the ratio of the k_1 and k_{-1} constants, the true rate constant (k') for the cyclization of imidazides is either the constant of the conformational transition ($k' = k_1$) or is the product $k' = k \cdot K_{eq}$, where $K_{eq} = k_1/k_{-1}$.

The activation parameters for the cyclization of a series of substituted N-phenylacetimidazides were presented in [29] (Table 1).

Close $\Delta H^{\neq}$ values were obtained during a study of the kinetics of cyclization of guanyl azide and nitroguanyl azide [34]. The activation parameters for the cyclization of N-phenylacetimidazides remain practically unchanged within the entire series. This is yet another conformation of the fact that the cyclization mechanism is the same for all of the indicated

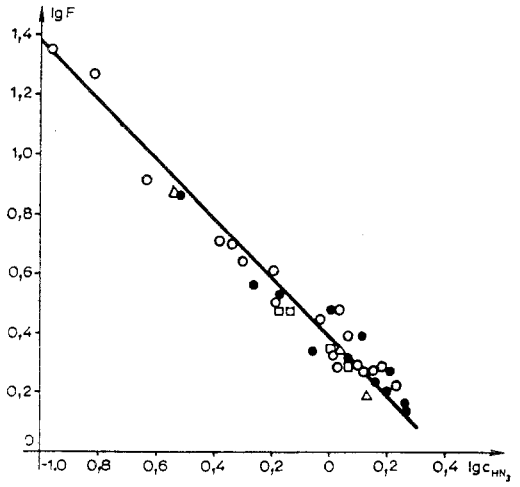


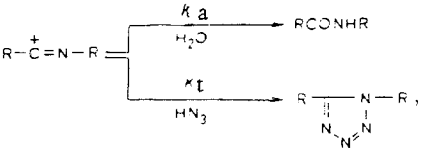
Fig. 3. Dependence of the amide/-tetrazole molar ratio on the hydrazoic acid concentration: ◒) 77.7; □) 83.1; △) 85.6' ○) 89.2; ●) 91.4% H_2SO_4.

compounds. However, one should take into account the fact that the mechanism for the cyclization of imidazides to tetrazoles may change as a function of the nature of the substituent attached to the carbon and nitrogen atoms. This should be expected primarily for sterically hindered imidazides and for imidazides with substituents containing strong electron-acceptor groups. The usual result when substituents of this sort are attached to the nitrogen atom is that imidazides undergo cyclization to tetrazoles with difficulty. As an example one may point to cyanoguanyl azide, which is converted to the corresponding 5-aminotetrazole only under the influence of strong bases [47].

Finally, it must be noted that aprotic acids are quite frequently used as catalysts in the preparation of tetrazoles from ketones and hydrazoic acid. There are not quantitative data available regarding the kinetics of such reactions. Nevertheless, one might assume that the mechanism of cyclization of imidazides to tetrazoles is the same for both protic and aprotic acids.

Amide/Tetrazole Ratio. As we have already noted, substituted amides are formed along with tetrazoles in the reaction of ketones with excess hydrazoic acid in the presence of catalysts such as sulfuric or hydrochloric acid. It might be assumed that the amide/tetrazole ratio should depend on the nature of the catalyst, the structure of the ketones, and the reaction conditions. However, there have been no systematic investigations in this direction. It is supposed that the absence of water in the reaction medium promotes the formation of tetrazoles [17, 48]. At the same time, there are known cases in which tetrazoles are obtained in satisfactory yields when the reaction is carried out in concentrated hydrochloric acid [49], although in earlier papers concentrated hydrochloric acid is recommended as a catalyst for the preparation of substituted amides [16].

A quantitative evaluation of the effect of the composition of the medium on the amide/tetrazole ratio was given in [50] in the case of the reaction of acetophenone with excess hydrazoic acid in aqueous sulfuric acid solutions. The formation of the amide and tetrazole can be represented as two parallel reactions



(14)

where k_α and k_t are the rate constants of the corresponding reactions. In this case the ratio of the rates of these reactions can be written

$$\frac{V_a}{V_t} = \frac{k_a \cdot f_{H_2O} \cdot c_{H_2O}}{k_t \cdot f_{HN_3} \cdot (c_{HN_3} - c_k)\,\alpha}, \qquad (15)$$

where f_{H_2O}, f_{HN_3}, c_{H_2O}, and c_{HN_3} are the activity coefficients and the concentration of water and hydrazoic acid, respectively, c_k is the concentration of the ketone and α is the mole fraction of unprotonated hydrazoic acid. For convenience, one can assume that $V_\alpha/V_t = A/T = F$ and $k_\alpha/k_t = k$, where A and T are the final concentrations of the amide and tetrazole. Under the condition $c_{HN_3} >> c_k$, expression (15) can be rewritten

$$F = K \frac{f_{H_2O} \cdot c_{H_2O}}{f_{HN_3} \cdot c_{HN_3}\,\alpha} \quad \text{or} \quad \lg F = \lg K + \lg \frac{f_{H_2O} \cdot c_{H_2O}}{f_{HN_3}\,\alpha} - \lg c_{HN_3} \qquad (16)$$

The activity coefficients of hydrazoic acid and the α_{H_2O}/α value do not change in 70-90% H_2SO_4 and are equal to 1 and 1.49, respectively [51, 52]. Thus the term log $(f_{H_2O} \cdot c_{H_2O})/(f_{HN_3} \cdot \alpha)$ in Eq. (16) is a constant. It follows from this that a linear dependence should

TABLE 1. Activation Parameters for the Cyclization of N-Aryl-acetimidazides $RC_6H_4N = C(N_3)CH_3$

R	*p*-OCH_3	*p*-CH_3	H	*p*-Cl	*m*-Cl	*m*-Br	*m*-NH_2	*m*-NO_2	*p*-NO_2
H_2SO_4 concn., %	32,7	48,6	50,8	50,9	50,7	50,7	48,8	52,4	58,6
$\Delta H^{\neq}$, kcal/mole	16,7	16,4	18,3	19,9	17,1	17,2	16,1	16,2	15,4
$\Delta S^{\neq}$, eu	−7,5	−13,1	−5,9	−8,9	−7,2	−7,3	−9,1	−8,5	−12,0

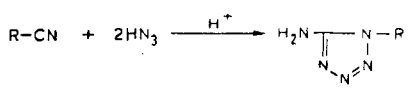
be observed between log F and log c_{HN_3} over the same acidity range of the medium and the amide/tetrazole ratio will depend only on the hydrazoic acid concentration. In fact, this sort of dependence is observed in 77.7-91.4% H_2SO_4 (Fig. 3). It is interesting that expression (16) is also valid at considerably higher hydrazoic acid concentrations (up to 1.8 M). It is not absolutely clear whether this sort of dependence will hold in those cases in which the reaction is carried out in aqueous solutions of other protic acids. For example, it can be shown that the log a_{H_2O}/α value does not remain constant in 60-75% $HClO_4$ [53]. The calculations were made under the condition that the activity coefficient and the pK_α value of hydrazoic acid are identical in sulfuric and perchloric acids. However, this condition is not always observed.

Aprotic acids are widely used as catalysts for the preparation of tetrazoles from ketones and hydrazoic acid. Tetrazoles are usually the only products under these conditions. At the same time, in some cases, for example, in the reaction of acetophenone with hydrazoic acid in the presence of aluminum chloride, N-phenyl-N'-methylurea is formed along with 1-phenyl-5-methyltetrazole [48]. Unfortunately, no quantitative data are available for reactions of this sort.

It is difficult to evaluate the effect of the structure of the ketone on the amide/tetrazole ratio on the basis of the available literature information. Practically all ketones, regardless of their structure, give mixtures of amides and tetrazoles on reactions with excess hydrazoic acid in the presence of aqueous solutions of mineral acids. Inasmuch as the reaction conditions presented by various authors are difficult to compare, it is impossible to observe any relationship between the structure of the starting ketone and the magnitude of the amide/tetrazole ratio. The only definite thing one can assert is that tetrazoles are formed in higher yields than amides from cyclic ketones.

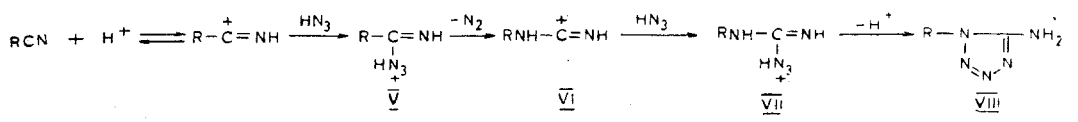
Preparation of 1-Alkyl- and 1-Aryl-5-aminotetrazoles from Nitriles

General Characteristics of the Reaction. One of the little-studied varieties of the Schmidt reaction is the reaction of nitriles with hydrazoic acid [54, 55]. Rearrangement occurs in the presence of acid catalysts such as sulfuric acid



This reaction is successfully used as a convenient one-step method for the preparation of 1-alkyl- and 1-aryl-5-aminotetrazoles from aliphatic and aromatic nitriles. There are no quantitative data available regarding the mechanism of the reaction of nitriles with hydrazoic acid; the available information is based on investigations of a synthetic nature. For this reason, the range of application of the reaction is difficult to fully evaluate.

Mechanism of the Reaction of Nitriles with Hydrazoic Acid. In analogy with ketones, the mechanism of the reaction of nitriles with hydrazoic acid can be represented by the following scheme [55]:



(17)

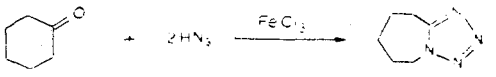
According to [17] an acid–base equilibrium between the starting reagents precedes the major process. The first step in the reaction is reaction of the protonated form of the nitrile with unprotonated hydrazoic acid. This gives imidazide V, the subsequent transformations of which give carbodiimide VI, azide VII, and tetrazole VIII.

It should be noted that the mechanism of the reaction constructed via the principle of analogies has substantial inadequacies. The weakness of this sort of interpretation is associated primarily with the absence of data on the kinetics of the reaction. Thus, it is unclear why imidazide V readily undergoes rearrangement to carbodiimide VI, whereas the imidazides formed in the reaction of ketones with excess hydrazoic acid in concentrated sulfuric acid are completely stable [28]. Other contradictions in this scheme can also be pointed out, but, insofar as we know, there is not a single paper in which proof for the validity of this reaction mechanism has been presented. Despite this, scheme (17) makes it possible to satisfactorily explain the available experimental data, although there are known cases [56] that do not fit within the framework of this reaction mechanism.

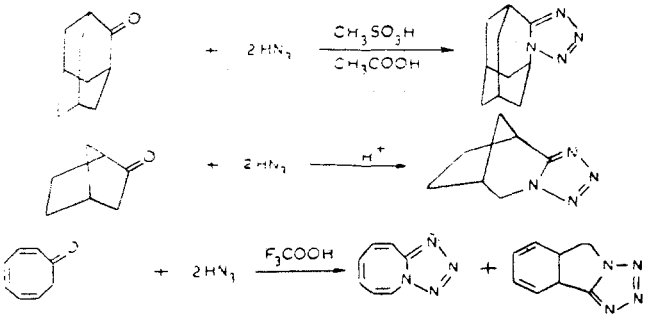
Scope of the Reaction

The reaction of ketones with hydrazoic acid is a convenient method for the preparation of mono- and disubstituted tetrazoles. In some cases, the Schmidt reaction gives excellent results when other methods are ineffective. Tetrazoles are obtained by means of this method in one step from accessible reagents under mild conditions. Protic and aprotic acids are used as catalysts for the Schmidt reaction. The most widely used catalyst is sulfuric acid [14, 57-59], but hydrochloric [49], methanesulfonic [60-62], and trifluoroacetic [60, 63] acids are also used. Aluminum chloride [16], ferric chloride [64], and stannic chloride [17] are extremely effective catalysts for the reaction of ketones with hydrazoic acid. The use of aprotic acids makes it possible to avoid the formation of amides, and the tetrazoles are obtained in high yields. One should also note the good results that were obtained with boron trifluoride etherate [65].

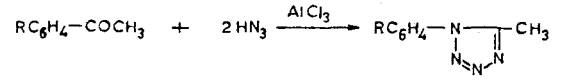
The Schmidt reaction with ketones and nitriles is carried out both with solutions of hydrazoic acid in an inert solvent and with sodium azide. It has been noted that the use of hydrazoic acid gives better results [59, 66], although sodium azide is a more convenient reagent. Ketones and nitriles of various structures readily undergo reaction with hydrazoic acid. 1,5-Disubstituted tetrazoles are formed from the simplest aliphatic ketones, for example, acetone [14] or diisobutyl ketone [67]. Under similar conditions cyclic ketones are converted to tetrazoles in higher yields [57, 64, 68]. Thus cyclohexanone gives pentamethylenetetrazole (Corazole), which has found application in clinical practice as an effective CNS stimulant [1, 69].



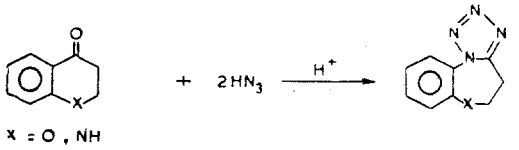
Cyclic ketones such as adamantanone [61], camphor [59], and 2,4,6-cyclooctatrienone [63] give the corresponding tetrazoles via the same method:



Alkyl aryl ketones react with excess hydrazoic acid to give 1-phenyl-5-alkyl tetrazoles [16, 48]:

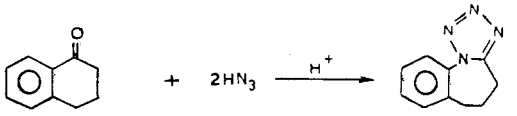


Tetrazoles are formed in higher yields from cyclic alkyl aryl ketones [49, 66]:



X = O, NH

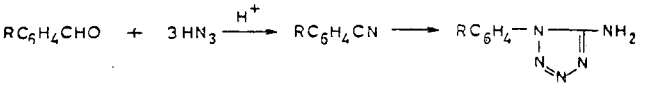
The presence of a heteroatom in the ketone molecule is not an obstacle to reaction with hydrazoic acid [58, 70]:



Ketones with more complex structures, for example, triterpenoids [15] and several others [65], are converted to tetrazoles, and other functional groups are not involved in this reaction.

Aliphatic and aromatic nitriles react with excess hydrazoic acid to give 1-alkyl- and 1-aryl-5-aminotetrazoles [54, 55]. Tetrazoles are usually obtained in lower yields from aromatic nitriles than from aliphatic derivatives. A mixture of mono- and ditetrazoles is formed from dinitriles [54].

1-Aryl-5-aminotetrazoles can be obtained by means of the Schmidt reaction directly from aldehydes without isolation of the intermediately formed nitriles [71, 72]:



The reaction of unsaturated nitriles with hydrazoic acid proceeds via a different path. Thus pyruvic acid is formed from acrylonitrile instead of the expected 1-vinyl-5-aminotetrazole [56].

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