HETEROGENEOUSLY CATALYTIC CYCLIZATION OF ARYLHYDRAZONES
TO INDOLES (REVIEW)

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The principles and peculiarities of the heterogeneously catalytic cyclization
of arylhydrazones to indoles are examined.

It is known that most compounds of the indole series can be obtained readily and simply by the Fischer reaction from the corresponding arylhydrazones. However, it has not yet been possible to obtain indole itself and its derivatives without substituents in the pyrrole ring by this method [1], whereas precisely these compounds are of particular interest for obtaining natural and physiologically active substances. The cyclization of various aryl-hydrazones to the corresponding indoles has hitherto been accomplished primarily by one of three methods: 1) the Fischer method using large amounts of condensing agents; 2) the Arbuzov method by decomposition of arylhydrazones in the presence of catalytic amounts of cuprous chloride; 3) thermal indolization. None of these methods was suitable for the solution of the indicated problem.

In the middle of the sixties in the Department of Organic Chemistry of D. I. Mendeleev Moscow Institute of Chemical Technology we began research on the heterogeneously catalytic cyclization of arylhydrazones that made it possible to accomplish the synthesis of indole [2] and a number of substituted indoles [3] and to determine the principles of the occurrence of this process.

Cyclization of Acetaldehyde Phenylhydrazone

Indole was obtained for the first time from acetaldehyde phenylhydrazone (I) under heterogeneous-catalysis conditions using γ-Al_2O_3 as the catalyst.
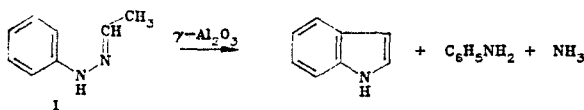
A number of other catalysts were subsequently tested: a mixed catalyst based on magnesium, zinc, and aluminum oxides, silica gel, zeolites, cuprous chloride on pumice, aluminum oxide with the addition of oxides of certain metals, and aluminum oxide treated with phosphoric acid or sodium hydroxide. The highest yield of indole was obtained when industrial aluminum oxide without any additives was used. The catalyst was first activated by calcination in a stream of air at 600-650°C for 3-4 h. The cyclization was carried out in a stream of nitrogen or carbon dioxide at a catalyst-layer temperature of 300-330°C. Hydrazone I was fed to the catalyst in a mixture with benzene in a mass ratio of 1:2. The yield of indole under these conditions was 56-60% [2].

A mathematical model of the process was obtained in subsequent research by means of factor planning; this made it possible to increase the yield of indole to 67% in the case of cyclization on aluminum oxide [4].

The industrial aluminum oxide used functioned without regeneration for several hours, after which it was easily regenerated by calcination in a stream of air at 600-650°C.

Co-workers of the State Institute of Applied Chemistry improved the process of cyclization of hydrazone I to indole by proposing the use of an aluminum-magnesium fluoride cata-

lyst that is a mixture of aluminum oxide and magnesium fluoride; this made it possible to increase the yield of indole to 85% based on the amount of hydrazone I introduced into the reactor [5]. The proposed catalyst functions without a substantial loss of activity for several hundred hours and is easily regenerated in a stream of air mixed with nitrogen by heating [6]. An algorithm for regulating the regeneration of the catalyst [7] and a special method for purification of the resulting indole [8] were developed.

All subsequent attempts to improve the cyclization of hydrazone I to indole did not lead to positive results. Thus Suvorov, Smushkevich, and co-workers accomplished this cyclization on the classical catalyst of the Fischer reaction — zinc chloride. At 220°C the conversion to indole was 24% [9]. In 1976 Japanese scientists realized the cyclization of hydrazone I to indole in a flow reactor at 290-300°C on zinc chloride applied to porous glass spheres. The catalyzate contained 36% indole and 46% aniline [10]. Indole was also obtained in 56% yield by cyclization of hydrazone I using a mixture of magnesium and silicon oxides as the catalyst [11].

Attempts were subsequently made to reduce the process to one step and synthesize indole directly from phenylhydrazine. In 1973 Japanese scientists developed a method for obtaining indole from phenylhydrazine and paraldehyde on aluminum oxide with an optimal yield of 68% [12]. Similar results were obtained when a mixture of silicon dioxide with manganese(IV) oxide or magnesium oxide was used [13, 14].

An attempt to obtain indole and some substituted indoles from phenylhydrazine and some vinyl ethers under hetrogeneous-catalysis conditions using an aluminum–magnesium fluoride catalyst did not lead to positive results [15].

Japanese scientists also accomplished the cyclization of hydrazone I to indole on other oxides. They established that η-Al_2O_3 is an active catalyst and makes it possible to obtain indole in 59% yield; however, the cyclization is accompanied by considerable decomposition of the hydrazone to aniline (35%). The most successful catalyst, which consists of silicon oxide and magnesium oxide, has weak acidic properties, while rapid loss of activity occurred on strongly acidic catalysts of the aluminum oxide–boron oxide, titanium(IV) oxide–silicon oxide, and zeolite type, and the reaction led primarily to the formation of aniline. The authors associated this with the fact that in the case of strongly acidic catalysts stronger absorption of the nitrogen-containing bases on the catalyst surface leads to retarded regeneration of the active centers [16].

A number of alkylindoles were obtained by the vapor-phase cyclocondensation of various carbonyl compounds and phenylhydrazine or aniline over aluminum orthophosphate. The best results were obtained in the reaction between lower aldehydes (propionaldehyde and butyraldehyde) and aniline. The yields of the corresponding indoles were 75% and 62%. 2,3-Trimethyleneindole was obtained in 45% yield from cyclopentanone and phenylhydrazine under the reaction conditions [17].

Kinetics of the Cyclization of Acetaldehyde Phenylhydrazone

The first studies of the kinetics of cyclization of hydrazone I under heterogeneous-catalysis conditions were accomplished for the process in a flow reactor on γ-Al_2O_3 using the Frost equation for irreversible, first-order, heterogeneous, catalytic reactions. The rate constants and the energies of activation for the cyclization of hydrazone I to indole and its decomposition to aniline were calculated on the basis of the results obtained and were found to be 33 and 41 kcal/mmole, respectively [4].

The investigation of the kinetics of these processes was subsequently continued by means of a gradient-free method in a reactor with a vibrationally fluidized bed of catalyst, viz., aluminum oxide [18]. It was observed that at all temperatures the rate initially depends linearly on the pressure of the acetaldehyde phenylhydrazone. This dependence is retained up to a pressure of 39.99 Pa at 280°C and up to 533.28-666.61 Pa at higher temperatures. Deviation from the linear dependence, which increases with a decrease in the temperature, begins with an increase in the pressure of the hydrazone. The reaction is a zero-order process at 280°C and a hydrazone pressure greater or equal to 533.28 Pa. The rate-determining step of the cyclization was determined by the method of nonsteady-state concentrations. On the basis of the data obtained it was concluded that the rate-determining step of the process is desorption of the reaction products from the catalyst, on the basis of which a kinetic scheme and the following reaction equation were proposed:

$$k = k_1 k_2 Z_T P_A / [k'_1 + k_2 + k_4 + (k_1 k_3 + k_1 k_2)/P_A/k_3],$$

where Z_T is the total number of active centers of the catalyst, and k_1, k_1', k_2, k_3, and k_4 are the rate constants for the adsorption of hydrazone I, its desorption from the catalyst, cyclization to indole, desorption of the products from the catalyst, and decomposition to aniline, respectively. The energy of activation was determined from the dependence of the reaction rate on the temperature and was found to be 33 ± 1.5 kcal/mole (hydrazone pressure 133.32-266.64 Pa).

A study of the kinetics of the cyclization of hydrazone I to indole in the vapor phase using an aluminum-magnesium fluoride catalyst in an adiabatic reactor of the tubular or column type made it possible to conclude that the rate of thermal decomposition of hydrazone I is described by a first-order equation [19]:

$$\lg k = -37\,000/4.575T - 13.1.$$

The rate of overall catalytic conversion of hydrazone I to indole and its decomposition to aniline and resin in the absence of diffusion inhibition is described by the equation

$$dX/d\tau = (k_1 + k_2)(1 - X),$$

where X is the overall degree of conversion of hydrazone I, τ is the time that the vapor phase resides in the reaction zone, and k_1 and k_2 are the rate constants of the principal and side reactions.

The rate constants of the reactions were determined:

$$\lg k_1 = (-19\,000 \pm 500)/4.575T \pm 7.8;$$
$$\lg k_2 = (-28\,500 \pm 800)/4.575T \pm 10.8.$$

On the basis of a mathematical description of the catalytic cyclization of hydrazone I and the regeneration of the catalyst the authors determined the principal parameters of the reactor unit for the manufacture of indole and developed a technological scheme that was verified on an experimental scale [20-22].

Research Using Labeled Atoms

It is known that the nitrogen atom that is farther away from the benzene ring of the arylhydrazone is split out in the form of ammonia under the conditions of the classical Fischer reaction. The cyclization of acetaldehyde phenylhydrazones containing ^{15}N was carried out to study this step in indolization under heterogeneous-catalysis conditions [23]. It was established that in this case, just as under homogeneous-catalysis conditions, the nitrogen atom that is farther away from the benzene ring is split out in the form of ammonia.

Deuterated indole containing 65-70% deuterium was obtained by the heterogeneously catalytic indolization of acetaldehyde phenylhydrazones containing deuterium labels in the ethylidene group [24].

The use of a tritium label showed that the label was distributed among all of the products (indole, aniline, and ammonia) and between the 2 and 3 positions and the benzene ring in indole. In aniline the label was located primarily in the benzene ring. The label was present in insignificant amounts in the imino and amino groups of indole; the authors assumed that this was a consequence of loss during isolation. On the basis of a comparison of the data obtained it was concluded that the amount of label in the 2 position of indole is determined to a great extent by migration of hydrogen from the 3 position. Redistribution of the tritium in starting hydrazone I prior to its cyclization to indole primarily affects the amount of label in the benzene ring of indole. The authors assume that migration of tritium in indole and H–T exchange of indole with aniline and ammonia occur [25, 26] and that one can explain the results obtained by using the known equilibrium between the phenylhydrazone and the enehydrazine. Protonation of the resulting enehydrazone and its cyclization lead to indole with labels in the benzene ring and in the 2 and 3 positions.
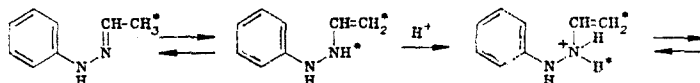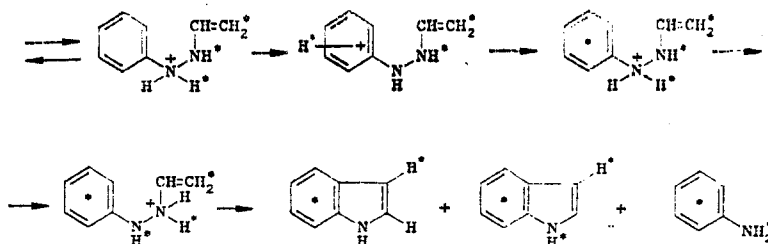
Cyclization of Other Arylhydrazones

Carrying out the cyclization of arylhydrazones under heterogeneous-catalysis conditions using aluminum oxide or an aluminum-magnesium fluoride catalyst as the catalyst made it possible to realize the cyclization of a number of other arylhydrazones that do not undergo cyclization under the conditions of the Fischer reaction (see Table 1).

Thus 5-chloro-, 5-methyl-, and 4-, 5-, 6-, and 7-methoxyindole and a number of other substituted indoles that contain substituents only in the benzene ring have been synthesized. One should particularly note the successful cyclization of acetaldehyde o-, m-, and p-methoxyphenylhydrazone to the corresponding indoles [27]. Heterogeneous catalysis made it possible to realize the cyclization of acetaldehyde 2-pyridylhydrazone and obtain 7-azaindole [28].

The synthesis of a number of indole compounds that contain an electron-acceptor group (CN, $COOC_2H_5$, Cl).

3-Phenylindole was obtained from phenylacetaldehyde phenylhydrazone under the conditions of heterogeneously catalytic cyclization; virtually no migration of the phenyl fragment to the 2 position occurred. 5-Methoxy-3-phenylindole was similarly obtained from phenylacetaldehyde p-methoxyphenylhydrazone [29].
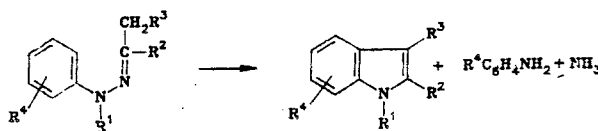

A significant number of the compounds presented in Table 1 were obtained for the first time from the corresponding arylhydrazones, thanks to the use of heterogeneous catalysis. For the same indoles that can be obtained under the conditions of the classical Fischer reaction the yields under the conditions of heterogeneously catalytic cyclization were considerably higher in most cases.

Only the nitro-substituted arylhydrazones constituted an exception. It was virtually impossible to accomplish their cyclization to the corresponding indoles. This is evidently associated with splitting out on the catalyst of the nitro group by the formation of nitrogen oxides, which are strong catalytic poisons. The presence of indole in the catalyzate is evidence for this sort of splitting out of the nitro group [30].

Splitting out of a methoxy group has also been noted in the heterogeneously catalytic cyclization of arylhydrazones [31].

The process involving dealkylation and anomalous cyclization with the formation of a triazole ring, which is accompanied by indolization of acetone 2-pyridylhydrazone, is interesting [35].
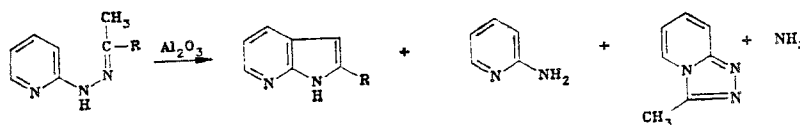
Relationship between the Catalytic Activity and the Physicochemical Properties of the Catalyst

The catalytic activity of aluminum oxide is associated with the existence of acidic centers on its surface [33]. In this connection the acidity of aluminum oxide was studied,

TABLE 1. Data on the Cyclization of Arylhydrazones under Heterogeneous-Catalysis Conditions

Indole obtained	Starting compound	Catalyst	T,°C	Yield, %	Literature
Indole	Acetaldehyde phenyl-hydrazone	Al_2O_3 $Al_2O_3+MgF_2$	300...330 270±5	60...65 85	[2,3] [5]
5-Chloroindole	Acetaldehyde 4-chloro-phenylhydrazone	Al_2O_3	330...340	45...48	[3]
4-Nitroindole 6-Nitroindole	Acetaldehyde 3-nitro-phenylhydrazone	$Al_2O_3+MgF_2$	300...320	1 1	[29]
5-Nitroindole	Acetaldehyde 4-nitro-phenylhydrazone	$Al_2O_3+MoF_2$	300...320	4	[30]
7-Nitroindole	Acetaldehyde 2-nitro-phenylhydrazone	$Al_2O_3+MgF_2$	300...320	1	[30]
1-Methylindole	Acetaldehyde N-methyl-phenylhydrazone	Al_2O_3	340...350	15	[3]
2-Methylindole	Acetone phenylhydrazone	Al_2O_3	320...330	80	[3]
5-Methylindole	Acetaldehyde 4-methyl-phenylhydrazone	Al_2O_3	340...350	40...42	[3]
2-Methyl-5-chloroindole	Acetone 4-chlorophenyl-hydrazone	Al_2O_3	340...350	65	[3]
5-Methoxyindole	Acetaldehyde 4-me-thoxyphenylhydrazone	Al_2O_3 $Al_2O_3+MgF_2$	280...300 180...200	15 50	[31] [27]
4- and 6-Me-thoxyindole	Acetaldehyde 3-methoxy-phenylhydrazone	Al_2O_3 $Al_2O_3+MgF_2$	280...300 260...280	10...15 80...85	[31] [27]
7-Methoxyindole	Acetaldehyde 2-methoxy-phenylhydrazone	Al_2O_3 $Al_2O_3+MgF_2$	280...300 260...280	8...10 40...45	[31] [27]
2,3-Dimethyl-indole	Methyl ethyl ketone phenylhydrazone	$Al_2O_3+MgF_2$	230...250	90...95	[32]
3-Ethylindole	Butyraldehyde phenyl-hydrazone	Al_2O_3	330...340	85	[3]
5-Ethylindole	Acetaldehyde 4-ethyl-phenylhydrazone	Al_2O_3	290...300	25	[33]
2-Methyl-5-methoxyindole	Acetone 4-methoxy-phenylhydrazone	Al_2O_3	330...340	50	[3]
1,2,3-Trimethyl-indole	Methyl ethyl ketone N-methyl-N-phenyl-hydrazone	$Al_2O_3+MgF_2$	280	60	[32]
1-Acetyl-2,3-dimethylindole	N,N'-Diacetyl-N-phenyl-N'-(2-buten-2-yl)hy-drazine	$Al_2O_3+MgF_2$	280	28	[32]
2,3-Dimethyl-1-ethylindole	Methyl ethyl ketone N-ethyl-N-phenylhydra-zone	$Al_2O_3+MgF_2$	280	45	[32]
2-Phenylindole	Acetophenone phenylhy-drazone	$Al_2O_3+MgF_2$	280	90	[34]
3-Phenylindole	Phenylacetaldehyde phenylhydrazone	$Al_2O_3+MgF_2$	190...210	40...45	[29]
5-Chloro-2-phenylindole	Acetophenone 4-chloro-phenylhydrazone	$Al_2O_3+MgF_2$	260...280	65	[34]
5-Nitro-2-phenylindole	Acetophenone 4-nitro-phenylhydrazone	$Al_2O_3+MgF_2$	300...320	1	[30]
2(4-Nitrophenyl) indole	4-Nitroacetophenone phenylhydrazone	$Al_2O_3+MgF_2$	300...320	1	[30]
5-Cyano-2-phenylindole	Acetophenone 4-cyano-phenylhydrazone	$Al_2O_3+MgF_2$	200...230	45	[34]
5-Methyl-2-phenylindole	Acetophenone 4-methoxy-phenylhydrazone	$Al_2O_3+MgF_2$	200...230	70	[34]
5-Methoxy-2-4(nitro-phenylindole	4-Nitroacetophenone 4-methoxyphenylhydrazone	$Al_2O_3+MgF_2$	200...230	0	[30]
5-Methoxy-2-phenylindole	Acetophenone 4-methoxy-phenylhydrazone	$Al_2O_3+MgF_2$	260...280	70	[34]
5-Methoxy-3-phenylindole	Phenylacetaldehyde 4-methoxyphenylhydrazone	$Al_2O_3+MgF_2$	190...200	30	[29]
2-(4-Methoxy-phenyl)indole	4-Methoxyacetophenone phenylhydrazone	$Al_2O_3+MgF_2$	260...280	90	[30]
2,3-Dimethyl-1-phenylindole	Methyl ethyl ketone di-phenylhydrazone	$Al_2O_3+MgF_2$	280	0	[32]
5-Carbethoxy-2-phenylindole	Acetophenone 4-carbe-thoxyphenylhydrazone	$Al_2O_3+MgF_2$	280...290	50...52	[29]
7-Azaindole	Acetaldehyde 2-pyridyl-hydrazone	Al_2O_3	450	15	[28]
2-Methyl-7-aza-indole	Acetone 2-pyridylhydra-zone	Al_2O_3	315	50	[28]

and the acidity of the catalyst was compared with its activity in the cyclization of hydrazone I [36]. By nonaqueous titration with butylamine in the presence of Hammett indicators it was established that there are acidic centers of medium strength on the surface of aluminum oxide that change the color of indicators at pK_a 2.3 and pK_a 3. The overall acidity of aluminum oxide calcined at 600°C was 0.25 meg/g. The dependence of the acidity of aluminum oxide on the calcination temperature has extremal character with a maximum at 600°C. The catalytic activity of aluminum oxide in the indolization of acetaldehyde phenylhydrazone

also depends similarly on the calcination temperature. A distinct correlation between the catalytic activity and the acidity of aluminum oxide was established.

It was shown by thermal desorption of ammonia that the surface of aluminum oxide has acidic centers of medium strength with E_{des} = 7.5 kcal/mole. This result is in good agreement with the data obtained by means of nonaqueous titration. It was also established that the decrease in the activity of the catalyst is associated with poisoning of the acidic centers [4].

The data on the increase in the catalytic activity with an increase in the acidity of aluminum oxide as a result of its heat treatment, on the decrease in the catalytic activity in the case of poisoning of the acidic centers, and on the inhibiting effect of alkali and the promoting effect of fluorine constitute evidence for a relationship between the catalytic activity of aluminum oxide in the reaction under consideration and the acidic properties of its surface. It was assumed that the determining role in this reaction belongs to Lewis centers [37]. This was confirmed by IR spectroscopic data on the high-temperature adsorption of pyridine, which showed the existence of aprotic centers on the surface of aluminum oxide, since absorption bands that are characteristic for coordination-bonded pyridine were observed in the IR spectrum, and absorption bands of proton-donor groups were absent [36].

The observed increase in the catalytic activity of aluminum oxide with the introduction of fluorine confirms the assumption of the determining role of aprotic centers in the reaction under consideration. The maximum catalytic activity is observed for a sample containing 4.8% fluorine. It is known that an increase in the amount of fluorine in aluminum oxide samples of more than 5% decreases the aprotic acidity. The observed high catalytic activity of aluminum oxide when protic centers are absent on its surface made it possible to conclude that the initial step in the indolization of hydrazone I is isomerization of the starting arylhydrazone to an enehydrazine on aprotic centers [367].

An interesting result was obtained in a study of the activities of oxide catalysts in the indolization of acetaldehyde methoxyphenylhydrazones [38]. The investigated oxides (~20) are less active than aluminum oxide; oxides of period IV transition elements have approximately the same very low activity. Copper oxide, the activity of which is somewhat higher, constitutes an exception. A good correlation between the catalytic activity and the metal—oxygen distance and a correlation between the catalytic activity and the width of the forbidden zone and the number of d electrons in transition elements were observed for the remaining investigated oxides. The absence of a dependence of the activity on the width of the forbidden zone and the number of electrons and the extremely low activities of period IV d metals indicate the low probability of a redox mechanism for this reaction. The dependence of the activities on the difference in the metal—oxygen electronegativities indicates first and foremost that the reaction proceeds via an acid-base mechanism. The correlation of the activity with the metal—oxygen distance makes it possible to assume that multiple-point adsorption of the hydrazone on the catalyst surface is present.

Effect of the Steric Factor in the Heterogeneously Catalytic Cyclization of Arylhydrazones

It is known that the enehydrazine form of hydrazones readily undergoes indolization both in the presence of a catalyst and without one [39, 40]; this is in complete agreement with the well-known Robinson mechanism. However, under heterogeneous-catalysis conditions the cyclization of N,N'-diacetyl-N-phenyl-N'-(2-buten-2-yl)hydrazine to the corresponding indole proceeded with considerably greater difficulty than the cyclization of the corresponding nonacylated hydrazone form. To explain this phenomenon it was assumed that under heterogeneous-catalysis conditions the step that determines the rate of the process is the adsorption of the starting hydrazone on the catalyst along the nitrogen—nitrogen bond. This assumption is in complete agreement with the data in [38] and explains the difficulty in the cyclization of the diacetyl(enehydrazine) by means of steric hindrance during adsorption in the catalyst.

Further studies confirmed the substantial effect of the steric factor [32]. Thus it was established that methyl ethyl ketone arylhydrazones are arranged in the following order with respect to their ability to undergo indolization under heterogeneous-catalysis conditions: phenylhydrazone > N-methyl-N-phenylhydrazone > N-ethyl-N-phenylhydrazone > diphenylhydrazone. Methyl ethyl ketone N,N-diphenylhydrazone, which was assumed to be the most sterically hindered compound with respect to adsorption, virtually did not undergo indoliza-

tion. An examination of Stuart-Briegleb molecular models showed that in the most favorable conformation for the formation of a carbon-carbon bond in the methyl ethyl ketone phenylhydrazone molecule the nitrogen-nitrogen bond is most accessible for adsorption on the catalyst as compared with methyl ethyl ketone N-substituted phenylhydrazones. Satisfactory adsorption of the diacetyl(enehydrazine) is possible only in the case of deacetylation of at least one nitrogen atom. In fact, methyl ethyl ketone N-acetyl-N-phenylhydrazone was detected in the reaction products. The subsequent indolization of this compound led to 1-acetyl-2,3-dimethylindole, which, together with 2,3-dimethylindole, was the principal reaction product. It was experimentally established that the 2,3-dimethylindole was formed due to both deacetylation of 1-acetyl-2,3-dimethylindole and complete deacetylation of the diacetyl(enehydrazine) and subsequent cyclization of the resulting hydrazone:
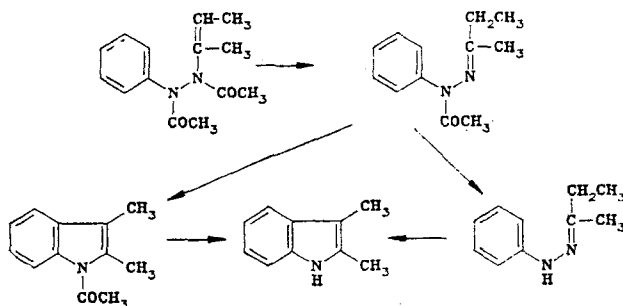
Effect of Electronic Factors in the Heterogeneously Catalytic Cyclization of Arylhydrazones

The mechanism of the cyclization of arylhydrazones to indoles still remains the subject of investigation by many scientists and cannot be considered to be definitively elucidated. Two principal points of view exist. According to the first point of view, indolization is assumed to be an intramolecular electrophilic process [41]; however, its consideration as a [3,3]-sigmatropic rearrangement [42] has recently become widespread. Despite the different opinions with respect to this question, one still has to acknowledge the fact that the presence of an electron-donor substituent in the benzene ring of the arylhydrazone significantly facilitates indolization under the conditions of the classical Fischer reaction.

An analysis of the indolization of various arylhydrazones under heterogeneous-catalysis conditions indicates that in this case the electronic factor plays a decisive role in the step involving adsorption of the arylhydrazone, decreasing or increasing the basicity of the latter. In the cyclization step, however, it evidently does not play such an important role. Thus the cyclization of arylhydrazones such as acetophenone p-methoxy-, p-chloro-, p-cyano-, and p-carbethoxyphenylhydrazone to the corresponding indoles, despite the presence of substituents with such different electronic effects, proceeds with commensurable yields (see Table 1). Consequently, the nature of the substituent in the benzene ring is not so much of a determining factor for the successful accomplishment of indolization as under the conditions of the classical Fischer reaction, in which there are always difficulties in obtaining indoles that contain electron-acceptor substituents in the benzene ring.

In this connection the certain degree of decrease in the yield of the corresponding indole when an acceptor subtituent is introduced into the benzene ring can be explained by a decrease in the basicity of the arylhydrazone and, as a consequence of this, by a decrease in the ability of this arylhydrazone to be adsorbed on the catalyst with subsequent indolization.

This correlation of the basicity and the ability to undergo cyclization to an indole has also been observed for a number of other arylhydrazones. Thus, in the case of the presence of a strong electron-acceptor substituent in the carbonyl component of p-nitroacetophenone phenylhydrazone conversion to the corresponding indole virtually does not occur, despite the fact that the nitro group in the carbonyl component should promote indolization via both an ionic mechanism and a sigmatropic-shift mechanism under the condition that adsorption along the nitrogen-nitrogen bond is not the determining factor, since a strongly polar transition state is evidently formed in each of these cases.

On the other hand, with the introduction of a methoxy group into the para position of the benzene ring of the carbonyl component one observes an increase in the basicity of the

arylhydrazone and, consequently, in its ability to be adsorbed on the active centers of the catalyst, and, as a consequence of this, the temperature optimum of the reaction decreases from 280°C to 240°C, and indolization proceed with good yields.

A similar correlation between the basicities of arylhydrazones and their ability to undergo cyclization to indoles is also observed for isomeric acetaldehyde methoxyphenylhydrazones [30].

Thus, the absence in the heterogeneously catalytic cyclization of a distinct correlation between the electronic nature of the substituents in the benzene ring of the arylhydrazone and its ability to undergo cyclization to an indole indicates that this is not an electrophilic process and, consequently, constitutes indirect evidence in favor of a sigmatropic rearrangement, although one cannot draw a definitive conclusion regarding this, since there is a strongly polar transition state in both the electrophilic process and in the sigmatropic rearrangement.

The heterogeneously catalytic cyclization of arylhydrazones makes it possible to obtain indole and substituted indoles that were previously inaccessible; the yields of the products are most often rather high. The isolation of the indoles from the catalyzates and their purification are quite simple processes. A number of principles that are characteristic for carrying out the classical Fischer reaction under homogeneous-catalysis conditions also remain valid for the heterogeneously catalytic indolization of arylhydrazones (the acidic character of the catalyst, splitting out of the nitrogen atom that is farthest away from the benzene ring during indolization). At the same time, heterogeneously catalytic indolization is also characterized by a number of peculiarities. Thus, multiple-point adsorption of the starting arylhydrazone on the catalytic centers is evidently necessary for the reaction to occur, and all of the factors that promote the successful realization of this process (the basicity of the arylhydrazone, the absence of steric hindrance) ultimately promote the cyclization of this arylhydrazone to the corresponding indole.

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