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Mechanism and Synthesis Potentialities of the Cyclization of *vic*-(Alkynyl)arenediazonium Salts

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Abstract

Cyclization of *vic*-alkynyl-substituted diazonium salts in the series of anthraquinone, naphthoquinone and benzene was studied. Basing on experimental data and the results of quantum chemical calculations, a scheme of heterocyclization mechanism was proposed for *vic*-(alkynyl)arenediazonium salts. The scheme proposed is fundamentally different from the generally accepted scheme of the Richter reaction mechanism.

Key words: cyclization, mechanism, *vic*-(alkynyl)arenediazonium salts, Richter reaction, indazoles, cinnolines

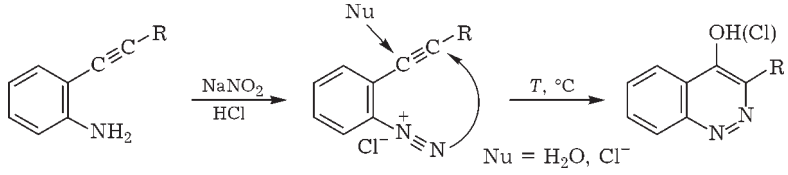
INTRODUCTION

Earlier the heterocyclization reaction of *vic*-(alkynyl)benzenediazonium salts discovered by Richter in 1883 [1] was used as a method for obtaining the derivatives of 4-hydroxy-4- chlorocinnoline [2]. However, studying the cyclization of 2-alkynyl-9,10-anthraquinone-1-diazonium chloride **1** demonstrated that the reaction in this case does not result in closing a six-membered pyridazine cycle, to occur with closing a five-membered pyrazole cycle [3]. Depending on the structure of alkynyl radicals, the reaction products are presented either by 1,1-dichloroalkyl-1H-naphtho[2,3-*g*]indazolediones **2** or acyl-1H-naphtho[2,3-*g*] indazolediones **3** [3]. The unusual behaviour of (alkynyl)anthraquinone diazonium salts in the cyclization reaction has forced the reconsideration of commonly accepted concepts concerning both the mechanism of this reaction and the synthetic potentialities of the latter.

The first attempts to create a hypothetical model of the Richter reaction mechanism were made by Schofield *et al.* [4, 5]. Their papers presented proper heterocyclization as a one-stage process that involves a simultaneous attack of the triple bond by a nucleophile (H_2O) and by the diazonium group, with anticipating the latter (Scheme 1).

Until recently, the scheme proposed did not undergo major changes, being fundamental when considering the mechanistic aspects of this reaction. At the same time, the scheme gave rise to more questions than answers. For example, it remained unclear why the electrophile (diazonium group) attacks the positively charged carbon atom of the triple bond, and the nucleophile, however, attacks the negatively charged carbon.

At the early stages of the investigation we have studied in detail the behaviour of 5-amino-6-(heptyne-1-yl)-3-diethylamino-1,4-naphthoquinone **4** in the diazotization and cyclization reactions [6, 7]. The choice of compound **4**



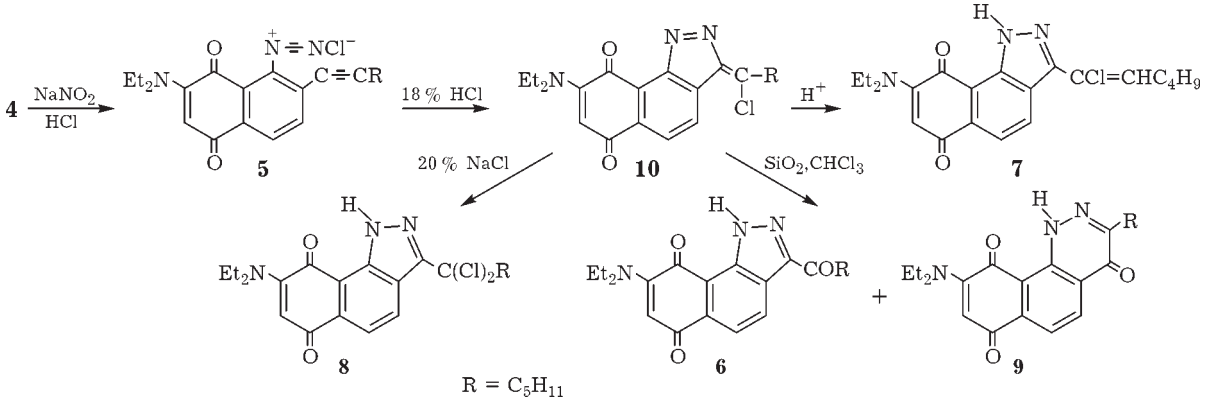
Scheme 1.

was not accidental. In the presence of the electron-donating diethylamino group in the quinonoid ring greatly reduces the influence of acceptor carbonyl groups. In the case when changing the direction of cyclization **1** is caused by electronic factors, the cyclization of the corresponding diazonium salt **5** of the amine **4** could be expected to yield the reaction products both with the five-membered, and with six-membered heterocycle.

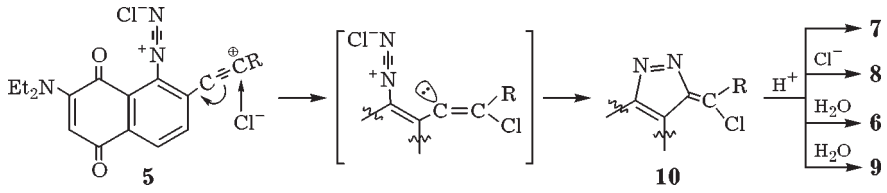
Getting to the study of the mechanism of cyclization, we have developed a novel method for carrying out the Richter reaction with separate the diazotization and cyclization processes. Earlier, the two processes were performed at one preparative stage within the same flask. The combination of a low acidity necessary for the diazotization stage, a high temperature inherent in the cyclization stage limited to a considerable extent entering the *vic*-amino(alkynyl)arenes into this reaction, those are sufficiently sensitive with respect to so severe reaction conditions. So, all the attempts for performing the cyclization of compound **4** with the use of this method resulted in failure due to a number of side processes, leading to a difficultly identifiable product mixture. For the separation of the stages it was necessary to organize such conditions of that the diazotization rate was much higher than the rate of cyclization. For this purpose, the diazotization of compound **4** was conducted at a room temperature in a water-acetone HCl solution with an excess of $NaNO_2$ (up to three times). Under such conditions, the diazotization finished just within the first minutes. The moment of time when the diazotization completed was monitored visually from changing the colour of the solution. Thereafter, the reaction mixture was rapidly diluted by 10 to 30-fold amount of water or NaCl solution or acid. Thus, the cyclization of compound **5** was performed under sufficiently mild conditions different from those inherent in the diazotization. Owing to the opportunity of independent varying the conditions of proper cyclization, the investigation of the mechanism of the mentioned reaction became convenient.

In the course of the investigations we revealed that, depending on the conditions the cyclization of compound **5** occurs with the formation of reaction products both with a five-membered heterocyclic structure (1*H*-8-diethylamino-3-(1-oxohexyl-1)-benz[*g*]indazole-6,9-dione **6**, 1*H*-8-diethylamino-3-(1-chloroheptene-1-yl)benz[*g*]indazole-6,9-dione **7** and 1*H*-3-(1,1-dichlorohexyl)diethylaminobenz-8-[*g*]indazole-6,9-dione **8**, and a six-membered heterocyclic structure such as 1*H*-9-diethylamino-3-pentylbenzo[h]cinnoline-4,7,10-trione **9** (Scheme 2). The structures of these compounds were confirmed by analytical and physicochemical methods.

It should be noted that we succeeded in matching the cyclization conditions, whereby a primary product of cyclization was obtained. Further, it was isolated, and its structure was unambiguously proven. This product represents a relatively stable compound with the structural formula such as 3*H*-8-diethylamino-3-(1-chlorohexylidene)benz[*g*]indazole-6,9-dione **10** (see Scheme 2). The investigation of its behaviour under different reaction conditions demonstrated that the conversion proceeds both with the conservation of the heterocycle size, and with the extension resulting in the formation of a six-membered pyridazine cycle. So,



Scheme 2.

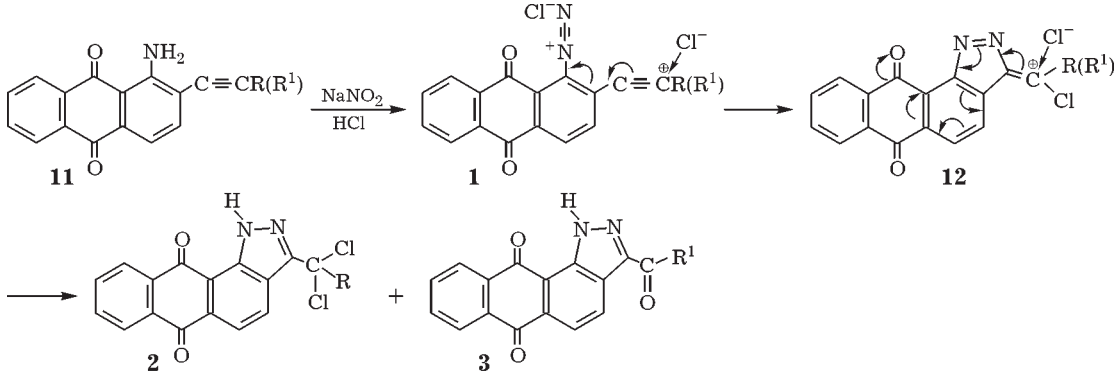


Scheme 3.

for example, in the course of 1*H*-8-diethylamino-3-(1-oxohexyl-1)benz[*g*]indazole-6,9-dione on silica gel in chloroform, compound **10** is entirely converted into a mixture of compounds **6** and **9**, with an approximate ratio amounting to 1 : 2. The fact that the conversion of the intermediate **10** with the extension of the initially formed 3*H*-pyrazole ring into the pyridazine ring became the fundamental one for understanding the essence of intramolecular mechanism for cycle formation processes in the case of *vic*-(alkynyl)-arenediazonium salts. Basis on the experimental data and quantum-chemical calculations we proposed a scheme for the mechanism of salt **5** cyclization (Scheme 3) [6, 7], that fundamentally differs from the scheme commonly accepted for the Richter reaction mechanism.

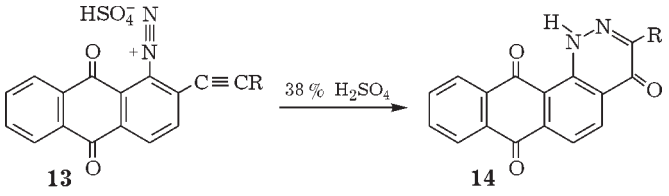
According to Scheme 3, the cycle formation process is initiated by a nucleophilic attack directed to β-carbon atom which is positively charged. The further alteration of the multiple bond hybridization with appearing an electron pair on the sp^2 hybrid orbital of α-carbon atom provides an opportunity for approaching the reaction centres to interact. As the result of such an interaction, the ring closure occurs with respect to α-carbon atom to form an intermediate containing five-membered heterocyclic ring with exocyclic double bond such as **10**. The direction of further transformations of the intermediate (either with the conservation, or with extension of the heterocycle size) depends on the conditions of cyclization. There is a good reason to believe that the cyclization of 2-alkynyl-9,10-anthraquinone-1-diazonium chlorides occurs within the framework of the same mechanism according to Scheme 4 [8].

One of the possible transformations of intermediate **12** with the conservation of the heterocycle size could consist in the interaction of the exo double bond with a nucleophile such as Cl^-. The likelihood that the process occurs for the anthraquinones is great enough due to a high electrophilicity of the exo-cyclic double bond caused by electron accepting properties of a quinoid nucleus. Ultimately, an 1,4-addition of HCl occurs with the formation of dichloro derivatives with the structure such as 1*H*-3-(1,1-dichloroalkyl)naphtho[2,3-*g*]indazole-6,11-diones **2** as it was found earlier. We established that owing to the nature of the structure some dichlorides can be rapidly hydrolyzed under the reaction conditions. The result obtained was an answer to the question why in the course of the heterocyclization of diazonium salts **1** in some cases we obtained dichlorides **2**, whereas



R = H, Bu, CH_2OPh; R^1 = Ph, COPr, COBu-*t*, COPh

Scheme 4.



R = H, Bu, C(OH)Me_2, CH(OH)Pr-*i*, CH(OH)Pr

Scheme 5.

in other cases we observed the formation of ketones **3**.

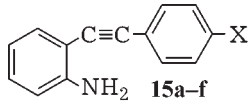
Deciding an issue concerning the possibility of obtaining the derivatives of naphthocinnolines in the mentioned reaction from *vic*-amino(alkynyl)quinones **11**, we excluded Cl^- as a strong nucleophile from the reaction mixture in the course of diazonium salt cyclization. With this purpose, in the course of compound **11** diazotization and the subsequent cyclization of the salt, we used dilute sulphuric acid instead of using hydrochloric acid [8].

Under these conditions, the role of a nucleophile is played by water molecule. It could be assumed that in this case, as it is for the cyclization of diazonium salt **5** under a high dilution level with water, the reaction product formed could represent a six-membered heterocycle. Indeed, in sulphuric acid we observed the formation of the reaction product mixture with five-membered heterocycle. It was established that the reaction directed to the extension of heterocycle is promoted by an increased acidity.

Increasing the concentration of acid at the cyclization stage up to 38 % allows directional obtaining the derivatives of naphthocinnolinetrione **14** with the yield ranging within 71–91 % (Scheme 5).

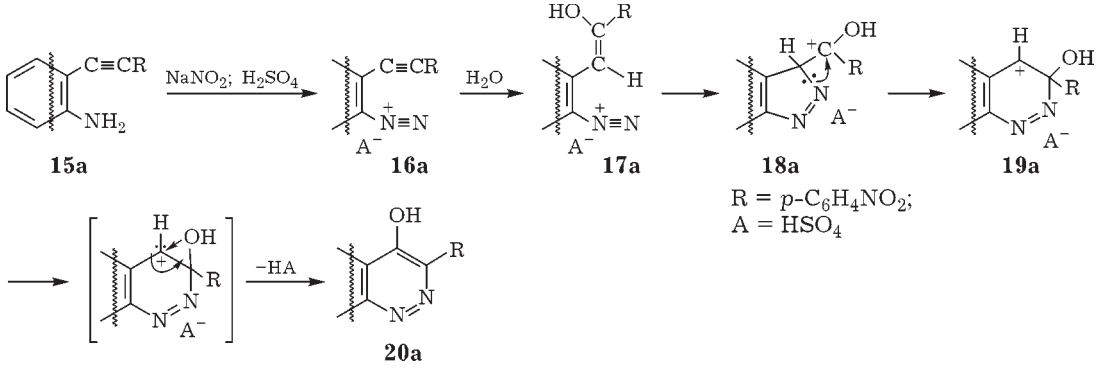
Thus, the studies concerning the transformation for mechanism *vic*-(alkynyl)arenediazonium salts in the series of quinones demonstrated that the cyclization process occurs in a multistage manner with the formation of a primary cyclization product containing 3*H* pyrazole ring. Within the framework of the mechanism proposed we demonstrated that *via* varying the reaction conditions, one could obtain condensed polycyclic quinoid structures containing either pyrazole or pyridazine cycle from the same *vic*-amino(alkynyl)-9,10-anthraquinones.

However, for creating a more complete picture for cyclization mechanism of *vic*-(alkynyl) arendiazonium salts we investigated this reaction for the benzene series [9, 10]. The diazotization and cyclization patterns were studied for a number of *ortho*-(phenylethynyl)anilines **15a–f**, with different substituents at the *para*-position of the phenyl ring (in parenthesis there is the value of electrophilic constant for substituents X presented):



15a–f

X = NO_2 (**a**) [+0.79]; H (**b**) [0]; $OCOCH_3$ (**c**) [−0.19]; $NHCOCH_3$ (**d**) [−0.60]; OCH_3 (**e**) [−0.78]; $N(CH_3)_2$ (**f**) [−1.7]



R = *p*-$C_6H_4NO_2$;
A = HSO_4

Scheme 6.

The criterion for choosing the substrates was presented by the value of electrophilic substituent constant for X (σ^+). The cyclization was carried out doth in hydrochloric acid, and in sulphuric acid. The studies performed demonstrated that the mechanism proposed for the cyclization of *vic*-(alkynyl)anthra diazonium and naphthodiazonium salts are of a general nature being realized for the benzene series. As it is in the series of quinines, the proper process of cycle formation begins after the interaction between the triple bond and a nucleophile to proceed with the formation of an intermediate having the structure of five-membered heterocycle. Further transformations occur either with the conservation of the heterocycle size, or with the heterocycle extension to form the derivatives of indazole or cinnoline as the reaction products, respectively. Either direction depends on the stability of the intermediate cyclic cation with a five- or six-membered ring. Scheme 6 illustrates the cyclization mechanism for *ortho*-(4-nitrophenylethinyl)aniline involving the isomerization of the intermediate cycle with its extension.

CONCLUSION

Thus, understanding the heterocyclization mechanism for *vic*-(alkynyl)arendiazonium salts makes it possible to control the Richter reaction in the case of different classes of compounds. Moreover, starting from the same initial amino *vic*-amino(alkynyl)arenes one could obtain condensed polycyclic structures containing either pyridazine or pyrazole ring.

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