



On the cyclization of *ortho*-alkynylbenzene diazonium salts

Lidiya G. Fedenok* and Nataliya A. Zolnikova

Institute of Chemical Kinetics and Combustion, Siberian Branch of Russian Academy of Sciences, Novosibirsk 630090, Russia

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Abstract—Cyclization of *ortho*-(phenylethynyl)benzene diazonium salts containing groups of +C character at the *para*-position of the phenyl ring proceeds with closure to a pyrazole, but not to a pyridazine as is the case in the presence of neutral or –C groups. © 2003 Elsevier Science Ltd. All rights reserved.

Earlier, it has been demonstrated that *ortho*-alkynylanilines can be diazotized and subsequently cyclized,¹ in one-pot, to give a pyridazine. These reactions have been used as a method of preparing cinnolines from *ortho*-alkynylanilines.^{2,3} Recently, it was shown that cyclization of 2-acetylenyl-9,10-anthraquinone-1-diazonium chloride proceeded with ring-closure to give a five-membered pyrazole and not the six-membered pyridazine.⁴ This result demonstrated that the synthetic potential of the cyclization of *ortho*-alkynylbenzene diazonium salts required further study. The key problem in the evaluation of the synthetic potential of this reaction was the elucidation of the relationship between the reactivity of the *ortho*-alkynylbenzene diazonium salts and their structure. There is an opinion that electron-withdrawing groups on the acetylenic substituent retard the cyclization whereas electron-donating groups accelerate it.⁵ In the same work it was reported that *ortho*-(4-dialkylaminophenylethynyl)benzene diazonium chlorides do not cyclize. Instead resinification and formation of a small amount of *ortho*-(4-dialkylaminophenylethynyl)phenol was recorded. The authors explained this fact as being due to protonation of the dialkylamino group, whereupon it acts as an electron acceptor. Such an explanation does not seem convincing, since the basicity of the dialkylamino group, which is in ‘push–pull’ conjugation with the diazonium group, is too low to be present in aqueous solution in a protonated state in any noticeable amounts. One would expect the influence of the conjugated electron-donating substituents of the dialkyl-

amino group to have a different effect on the cyclization process.

We studied the behavior of *ortho*-(4-dimethylaminophenylethynyl)aniline **1a** in diazotization and cyclization reactions. One would expect that elucidation of the causes that hinder the cyclization of the diazonium salt **2a** would make it possible to obtain a general idea of the relationship between the structure of the *ortho*-alkynylbenzene diazonium salts and the specificity of their behavior in cyclization reactions. In the present work, the method of separating the diazotization and cyclization reactions, proposed by us earlier when studying the cyclization of *vic*-aminoacetylenylquinones, was used.^{6,7} This method makes it possible to vary independently both the diazotization and the cyclization conditions.

In the course of our studies, it was found that the negative result obtained in Ref. 5 was determined not by the cyclization reaction, but by the diazotization. In this work, diazotization of **1a** was carried out in concentrated HCl. The presence in the molecule of a conjugated dimethylamino group, having a high electrophilic constant ($\sigma^+ = -1.7$),⁸ increases considerably the basicity of the aniline, which results in considerable protonation. This retards the diazotization process in which the free base takes part. Moreover, the simultaneous presence of a diazonium salt and an aniline activated by the dimethylamino group favors azo-coupling. As a result nearly insoluble, colored, polymeric azo-coupling products were formed. We established that a decrease in the HCl concentration at the diazotization stage to 6% considerably accelerated the reaction and gave the diazonium salt without any side reactions (solvent: water–acetone 1:2; 50% excess of

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* Corresponding author.

NaNO_2 ; -10 to -5°C). The diazonium salt formed was rapidly diluted (ca. 15-fold) with either water or concentrated NaCl or HCl solution. In the two former cases, cyclization was complete within less than 5 min.

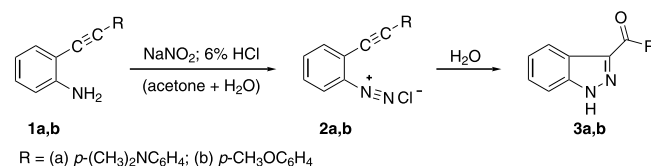
In concentrated acid, the reaction proceeded more slowly and was complete in 2 h.

In all the cases, the same product **3a** was obtained (mp 219 – 220°C). The IR spectrum showed that absorption bands due to $\text{C}\equiv\text{C}$ (2210 cm^{-1}) and NH_2 (3390 and 3490 cm^{-1}) were absent and that characteristic absorption bands at 1628 cm^{-1} ($\text{C}=\text{O}$) and 3459 cm^{-1} (NH) had appeared. The data obtained proved that cyclization had taken place and that the reaction product was either a derivative of 4-hydroxycinnoline, or a derivative of 3-benzoylindazole. It was not possible to identify the exact product by IR or NMR spectroscopy. Detailed and complete information regarding the size of the heterocycle was obtained with the aid of mass spectroscopy. In the mass spectrum of the cyclization product (Fig. 1), apart from the peak corresponding to the molecular ion M^+ (265), there was a peak due to a benzoyl ion $(\text{CH}_3)_2\text{NC}_6\text{H}_4\text{CO}^+$ (148). This demonstrated that the isolated compound **3a**⁹ possessed a five-membered heterocyclic structure, and that the reaction proceeded according to Scheme 1.

The non-trivial character of this result obtained prompted us to study the behavior, in this reaction, of *ortho*-(phenylethynyl)aniline **1b** containing, a *p*-methoxy substituted phenyl ring, CH_3O being similar in electronic character to $\text{N}(\text{Me})_2$. The electrophilic constant for the methoxy group is -0.78 .⁸ In Figure 2, the mass spectrum of the product obtained confirms the

five-membered structure **3b** for the heterocyclic product. Analogous to the mass spectrum of **3a** the intense signal of the benzoyl cation $\text{CH}_3\text{OC}_6\text{H}_4\text{CO}^+$ (135) is apparent confirming the position of the carbonyl group in the side chain of the pyrazole ring. It is noteworthy that in both cases the yield of cyclization products is high ($>80\%$). At the same time, it was necessary to obtain proof that the direction of the reaction was determined by the specificity of the electron-donating substituents and not by the chosen diazotization and cyclization conditions. Therefore, we studied, under the same reaction conditions, the behavior of the *ortho*-phenylethynylaniline **1c** containing the strongly electron-withdrawing NO_2 group. The resulting diazonium chloride **2c** was cyclized as before to give 3-(4-nitrophenyl)-4-chlorocinnoline **4c**⁹ according to Scheme 2.

Thus, it has been established that cyclization of *ortho*-alkynylbenzene diazonium salts, contrary to generally accepted notions, can proceed with the formation of six- and also five-membered heterocyclic rings. It has been demonstrated that the formation of the latter is promoted by the presence of a group of $+C$ character in the conjugated system of the acetylenic substituent.



Scheme 1.

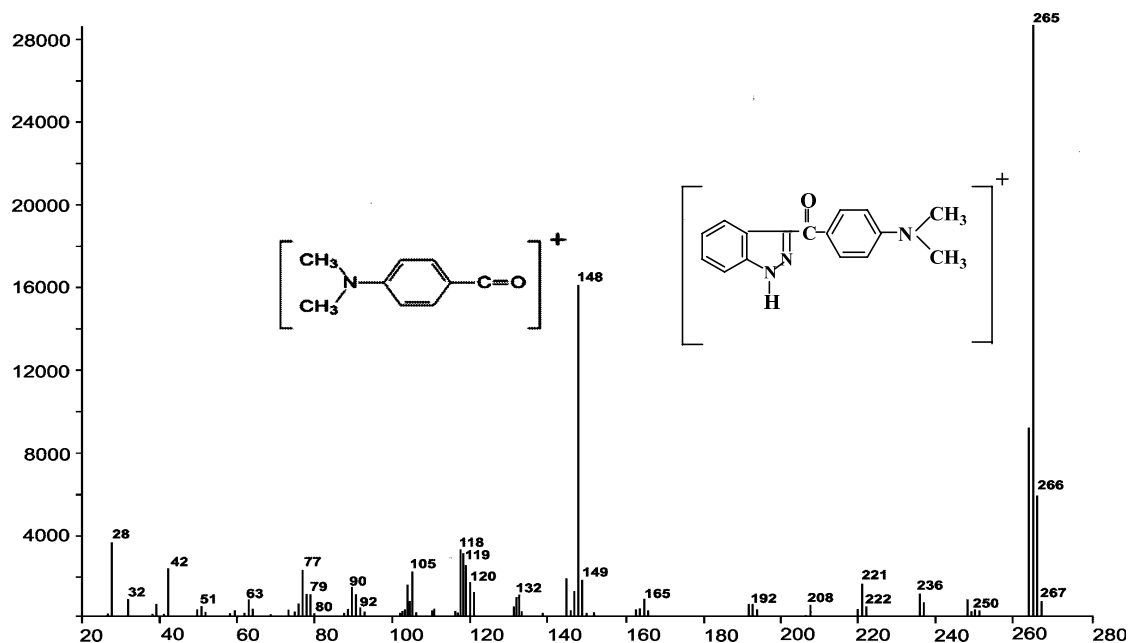


Figure 1. Mass spectrum of 3-(4-dimethylaminobenzoyl)indazole **3a**.

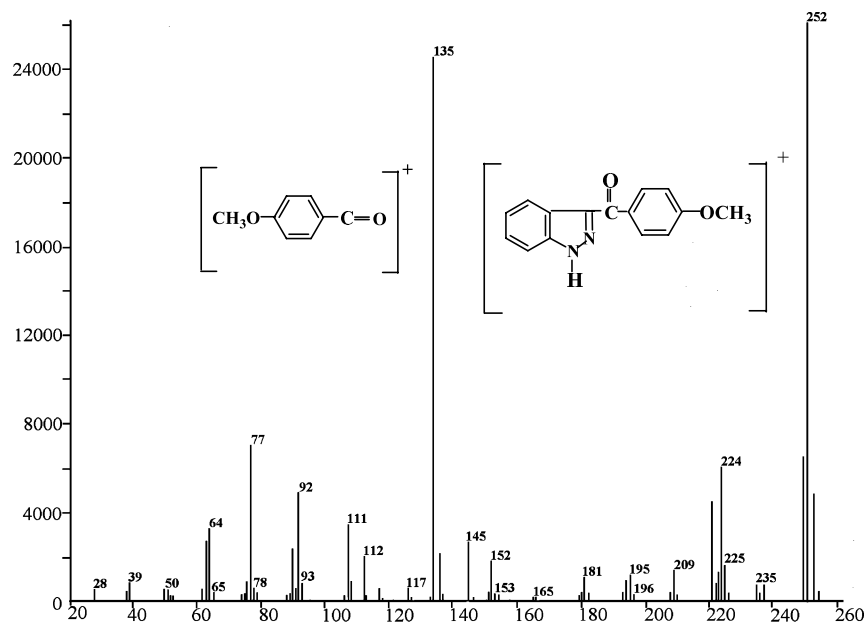
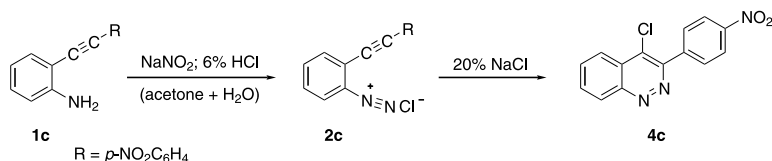


Figure 2. Mass spectrum of 3-(4-methoxybenzoyl)indazole **3b**.



Scheme 2.

Acknowledgements

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9. All compounds gave satisfactory analytical and spectroscopic data. **3a,b**, **4c** are given below. **3a** (mp 219–220°C): δ (CDCl₃) 3.05 (s, 6H, N(CH₃)₂), 6.74 (d, J =9.0 Hz, 2H, H-3',5'), 7.30–7.60 (m, 3H, H-4,5,6), 8.35 (d, J =9.0 Hz, 2H, H-2',6'), 8.43 (d, J =8.0 Hz, 1H, H-7), 10.45 (br.s, 1H, NH). **3b** (mp 167–168°C): 3.90 (s, 3H, OCH₃), 6.99 (d, J =8.8 Hz, 2H, H-3',5'), 7.30–7.60 (m, 3H, H-4,5,6), 8.38 (d, J =8.8 Hz, 2H, H-2',6'), 8.46 (d, J =8.1 Hz, 1H, H-7), 10.40 (br.s, 1H, NH). **4c** (mp 221–222°C; mp is higher by 43°C than in Ref. 5, hence **4c** has been recharacterized): 7.92–8.03 (m, 2H, H-6,7), 8.13 (d, J =7.6 Hz, 2H, H-2',6'), 8.31–8.37 (m, 1H, H-5), 8.43 (d, J =7.6 Hz, 2H, H-3',5'), 8.62–8.68 (m, 1H, H-8).