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The effect of substrate structure on the direction of cyclization of *ortho*-alkynylbenzene diazonium salts

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ABSTRACT

The cyclization of *ortho*-(arylethynyl)benzene diazonium salts (the Richter reaction) is studied. A reaction mechanism, which differs radically from that reported earlier is proposed and substantiated by experimental data and quantum-chemical calculations.

The cyclization of *ortho*-alkynylbenzene diazonium chlorides (the Richter reaction) has been used as a method for the preparation of cinnoline derivatives.[1,2] In a previous Letter, we reported that in some cases, this reaction proceeds via five-membered ring-closure to yield 3-(acyl)indazole derivatives **1** (Scheme 1).[3] This reaction is favored by strong +M functional groups at position 4 of the phenyl ring of the acetylenic substituent. However, the cyclization of diazonium salts **2**, containing acceptor, neutral, or weak donor substituents, leads to chlorocinnoline derivatives **4d–f** under the same conditions (Scheme 1).[3,4]

The goal of the present work is to elucidate the reasons for the different reaction pathways. According to literature data, the mechanism of the Richter reaction is interpreted as a one-step process.[2,5,6] It involves intramolecular coordination of the diazonium group with the β-carbon of the acetylenic substituent together with simultaneous attack of the nucleophile on the α-carbon. Chloride usually plays the role of nucleophile, although participation of water as the nucleophile cannot be excluded. This theory, however, gives rise to doubts, as it assumes the possibility of intramolecular interaction between the linear and spatially distant diazo- and ethynyl groups. It is reasonable to assume that the process is initiated by the nucleophile, which attacks the β-carbon rather than the α-carbon of the triple bond. Evidently, this interaction leads to the formation of a five-membered ring. If this is the case, it is necessary to understand why the five-membered ring is formed in one case and expands to a six-membered ring in the other case. In addition, the five-membered heterocyclic product contains no Cl atom, although the reaction proceeds under mild conditions in the presence of excess Cl^-. In order to investigate these points, we calculated the Mulliken charge distribution over carbon atoms C-1, C-2, and C-3 (Fig. 1) in substrates **2a–f**, employing the AM1 technique[7] using the MOPAC program.[8] To estimate the electronic properties of the substituents, the electrophilic constants σ_p^+ were used (Table 1).

Analysis of the calculated data shows that the triple bond polarization increases with enhancement of the electron-donating properties of the substituents (Table 2). Simultaneously, the electron density on C-3 increases. As follows from Table 2, the total charge on all three atoms is negative and almost doubles from **2f** to **2a**. The increase in the electron density on C-1 and C-3 hinders the approach of the Cl^- nucleophile.

At the same time, this charge distribution can favor interaction between the triple bond and a molecule of water. Diazotization of anilines **3a–f** and cyclization of the corresponding diazonium sulfates **5a–f** in dilute sulfuric acid were studied to elucidate information on the cyclization of *vic*-(alkynyl)benzene diazonium salts with participation of water as the nucleophile. The method of separating the diazotization and cyclization steps, as elaborated by us earlier,[3,4] was used. Diazonium salts **5a–f** were cyclized in aqueous H_2SO_4 of various concentrations at 25 °C and 45 °C. The following were established:

1. Diazonium salts **5a–c** are cyclized to 3-benzoylindazoles **1a–c** at the same rate as **2a–c** in 20% NaCl (~5 min, 25 °C).

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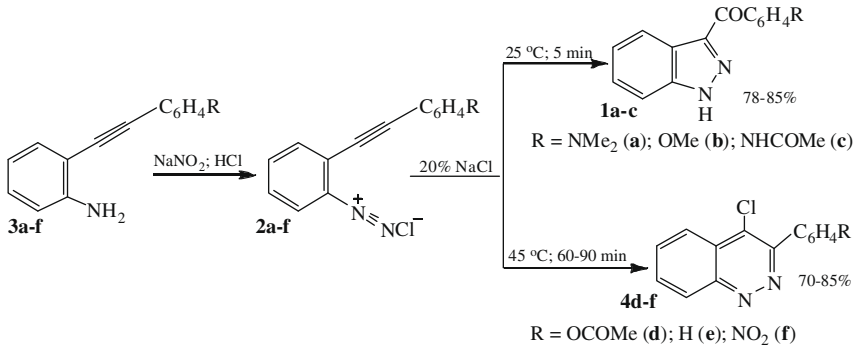


Scheme 1.

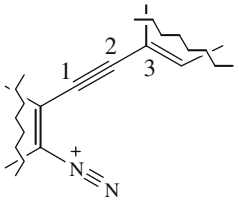


Figure 1. Carbon atom numbering of the diazonium cation.

Table 2
Charge distribution on C-1, C-2, and C-3 in diazonium cations **2a–f**

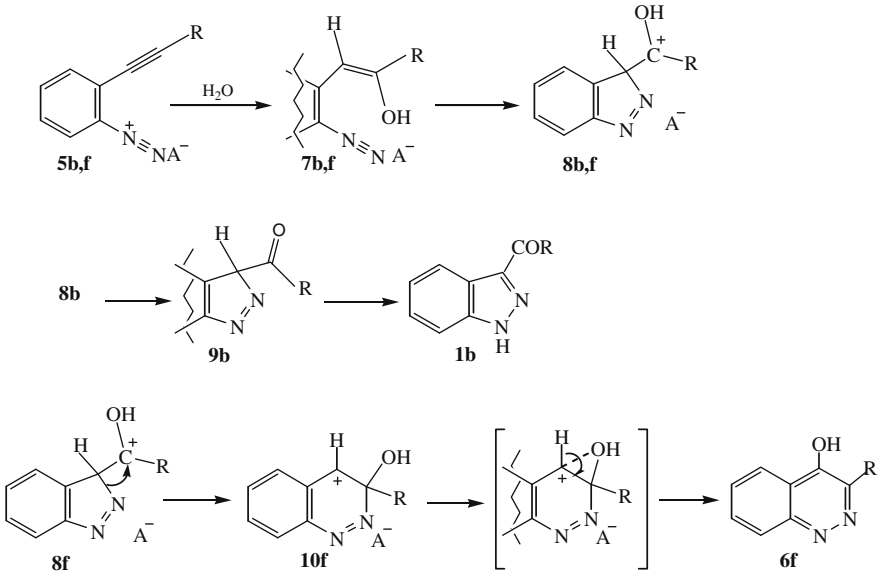
Compound	δ−C-1	δ+C-2	δ−C-3	Total charge on C-1, C-2, C-3
2a	0.32	0.12	0.15	−0.35
2b	0.30	0.10	0.10	−0.30
2c	0.29	0.10	0.09	−0.28
2d	0.28	0.09	0.07	−0.26
2e	0.28	0.09	0.05	−0.24
2f	0.24	0.05	0.00	−0.19

Table 1
The electrophilic constants σ_p^+ of the substituents in **2a–f**[9]

R	NMe_2 (**2a**)	OMe (**2b**)	NHAc (**2c**)	OAc (**2d**)	H (**2e**)	NO_2 (**2f**)
σ_p^+	−1.70	−0.78	−0.60	−0.19	0	+0.79

2. The cyclization of diazonium salts **5d–f** is 10 times slower than that of **2d–f** in 20% NaCl (~10 h, 45 °C). The cyclization of **5f** affords the six-membered heterocycle, 3-(4-nitrophenyl)-4-hydroxycinnoline **6f**. Diazonium salts **5d**, **e** form a mixture of **1** and **6** in a ratio of 1:2.
3. The rate of cyclization of all the compounds of a series is independent of the sulfuric acid concentration.

Experimental data are in fair agreement with the proposed mechanism presented in Scheme 2. It includes addition of water to the alkyne triple bond and subsequent cyclization to form cationic intermediate **8** containing a five-membered heterocycle. Scheme 2 also shows the transformations of substrates **5b** and **5f** having



R = *p*-$MeOC_6H_4$ (**b**), *p*-$NO_2C_6H_4$ (**f**)

A = HSO_4

Scheme 2. A mechanism for the cyclization of diazonium salts **5b** and **5f** in H_2SO_4.

Table 3
The values of ΔH_1 and ΔH_2 for the cyclization of **5a–f**

Compound	5a	5b	5c	5d	5e	5f
ΔH_1 kcal/mol	−19.5	−12.9	−15.1	−11.4	−5.1	+1.3
ΔH_2 kcal/mol	+3.1	+12.3	+14.6	+10.1	+4.7	−0.37

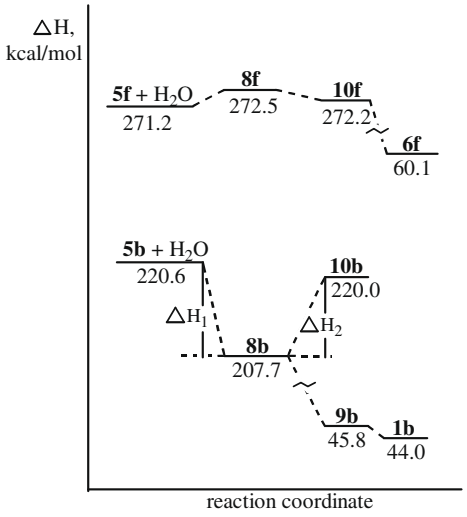


Figure 2. Thermodynamic characteristics for the cyclizations of **5b** and **5f** in H_2SO_4.

substituents of opposite electronic character (OMe, NO_2). In both cases, the reaction is regioselective, that is, **5b** only produces the five-membered pyrazole and **5f** the six-membered pyridazine. Calculations using the same technique AM1 indicate that the formation of adducts **7a–f** from diazonium salts **5a–f** is thermodynamically advantageous. The energy gain in the series of substrates varies from 13 to 25 kcal/mol. The addition of water changes the linear geometry of the acetylenic substituents and the reaction centers approach each other leading to cyclization at the α-carbon atom of the multiple bond. Table 3 summarizes the enthalpy values for the transformation of diazonium cations **5a–f** into cyclic cations **8a–f** (ΔH_1). ΔH_1 varies within a wide range from +1.3 kcal/mol for **5f** to −19.5 kcal/mol for **5a**. It is likely, that in this case, the thermodynamic characteristics of the process correlate with the values of the activation barriers, thereby determining its kinetic characteristics.

This assumption is in agreement with the fact that the reactivity of the substrates varies in parallel with the change in reaction enthalpy. Further transformations of cyclic cations **8b** and **8f** depend on the electronic character of the R substituent. Cation **8b** maintains the five-membered heterocycle, while cation **8f** isomerizes to form the six-membered product (Scheme 2). It should be noted that the final products, containing the six-membered heterocycle, are always on average 25 kcal/mol more stable than the reaction products containing the five-membered heterocycle. Nevertheless, the cyclization of diazonium salts **5a–c** yields reaction products containing five-membered heterocycles. The reason for this can be explained by the difference in the energy profiles of the transformation of diazonium salts **5b** and **5f** as shown in Figure 2. The direction of the process is likely to depend on the comparative stability of cations **8** and **10**. Due to conjugation with the electron-donating methoxy group, cation **8b** is more stable than **10b**

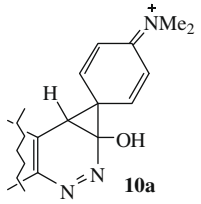


Figure 3. The assumed structure of cation **10a**.

Table 4
The charge (δ+) on C-2 of cyclic cations **8a–f**

Compound	8a	8b	8c	8d	8e	8f
δ+C-2	0.13	0.34	0.33	0.35	0.40	0.41

by 12.3 kcal/mol. Therefore it does not isomerize into **10b**, but is stabilized by elimination of H^+ from the hydroxy group to give ketone **9b**. After tautomerization, **9b** is transformed into the final stable 3-(4-methoxybenzoyl)indazole product **1b**. In contrast, the distribution of charges in cation **8f** favors rearrangement, resulting in heterocycle expansion. A subsequent 1,2-shift of the hydroxy group and aromatization lead to the final product, 4-hydroxycinnoline **6f**. Table 3 lists the enthalpy differences (ΔH_2) for the formation of the five- and six-membered cations. We propose that ΔH_2 can be used as a parameter for prediction of the direction of cyclization. It is interesting that ΔH_2 for the substrate with the NMe_2 substituent is low. This is probably due to the NMe_2 group being a strong electron-donor, which can stabilize the six-membered cyclic cation **10a** by forming a bridged structure (Fig. 3).

Nevertheless, indazole **1a** is the sole product of cyclization of diazonium salt **5a**. Expansion of the pyrazole ring in **8a** is apparently hampered by the low value of δ+ on C-2 in **8a** (Table 4). Hence, the direction of cyclization can be predicted by taking into account both ΔH_2 and δ+ on C-2 in cation **8**.

In conclusion, this study on the cyclization of *ortho*-(arylethynyl)benzene diazonium salts proposes a new cyclization mechanism, which differs radically from that reported earlier. The new mechanism explains the possibility of the formation of both cinnolines and indazoles in the Richter reaction. The ability to predict the mode of cyclization by means of simple quantum-chemical calculations was demonstrated.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.078.

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