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Two routes of heterocyclization of 2-alkynylanthraquinone-1-diazonium salts. The synthesis of 1*H*-naphtho[2,3-*h*]cinnoline-4,7,12-trione

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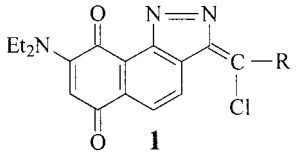
Abstract—The possibility of the heterocyclization of *vic*-alkynylanthraquinonediazonium salts with the formation of a 5- or 6-membered ring, depending on the reaction conditions, is established. The heterocyclization of 2-alkynyl-9,10-anthraquinone-1-diazonium salts to form 1*H*-naphtho[2,3-*h*]cinnoline-4,7,12-triones is reported.

1. Introduction

The cyclization of 2-alkynyl-9,10-anthraquinone-1-diazonium chlorides was demonstrated[1] to proceed with the formation of a 5-membered pyrazole ring and not a 6-membered pyridazine as in the benzene series (the Richter reaction).[2] This difference prompted us to reinvestigate both the mechanism of this reaction and its synthetic possibilities. We proposed another reaction mechanism.[3] According to this, heterocyclization is initiated by a nucleophilic agent (Cl^-, H_2O) attacking the polarized β carbon atom of the triple bond. The attack determines the formation of a ring with the participation of the α carbon atom. As a result, an intermediate is formed which contains a 5-membered heterocycle with an *exo*-cyclic double bond. Further transformations of the intermediate can proceed either with the conservation of the 5-membered ring or with its transformation into a 6-membered ring. The routes of these transformations are governed by both the structure of the intermediate and the properties of the environment. The same factors also define the stationary concentration of the intermediate, which can be very low in some cases. We succeeded in detecting, isolating and characterizing the primary product **1** of the cyclization of 3-diethylamino-6-(heptyn-1-yl)-1,4-naphthoquinone-5-diazonium chloride.[3]



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In order to vary the conditions in which cyclization occurs, we separated the stages of diazotization and cyclization. This was achieved by diazotization using a large excess of $NaNO_2$. The resulting diazonium salt was then quickly diluted with water or aqueous solutions of different salts, acids, etc. As a result, the cyclization itself took place under conditions different from those of diazotization. We used this heterocyclization technique[3] in the present work.

Here we describe an attempt to interpret the data obtained previously,[1] when the final product of cyclization was a 5-membered pyrazole cycle. Along with this, we searched for conditions under which the heterocyclization of 2-alkynyl-9,10-anthraquinone-1-diazonium salts affords a 6-membered heterocycle.

2. Results and discussion

With the above mechanism, it seems possible to explain an unusual route of cyclization of diazonium salts **3** (Scheme 1). One transformation of the intermediate **4** with the conservation of the heterocycle size is its interaction with the nucleophilic agent Cl^-. The probability of this reaction occurring is substantial for anthraquinones due to the electrophilic properties of the *exo*-double bond conjugated to the quinoid nucleus. As a result of interaction of **4** with Cl^-, either dichloroderivatives **5** or ketones **6** may be formed,

Keywords: Richter reaction; *ortho*-alkynylarenediazonium salts; heterocyclization; 3-substituted naphthoindazolediones and naphthocinnoline-triones.

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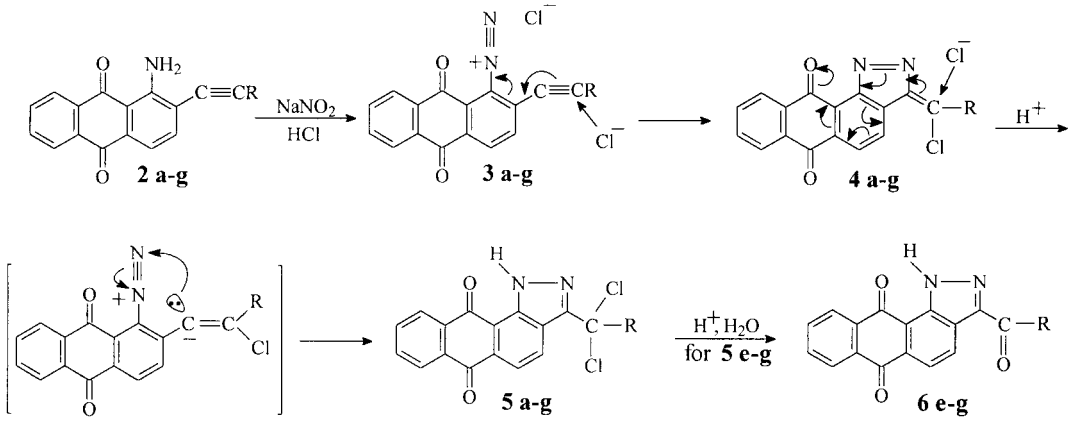
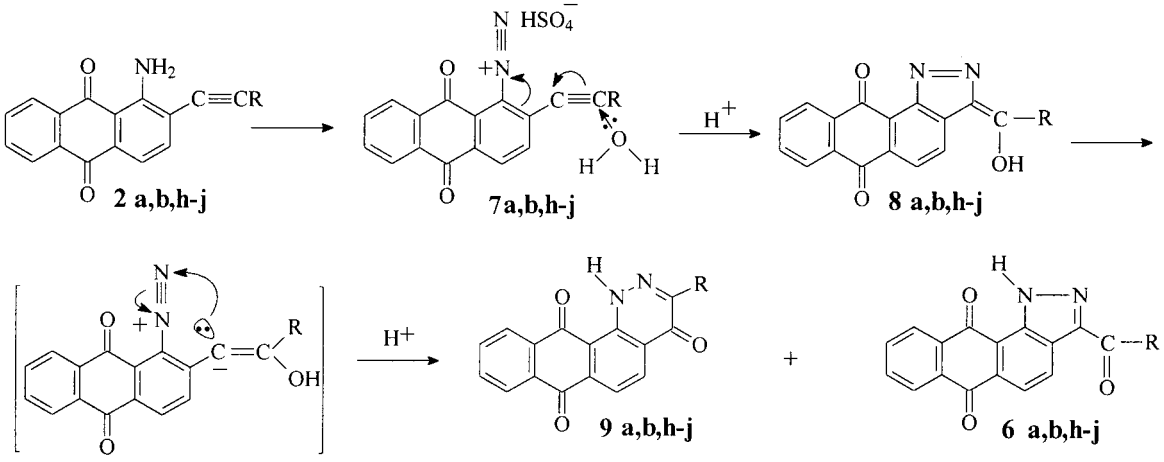


Scheme 1. a: R=H; b: R=Bu; c: R=CH_2OPh; d: R=1-HO-*cyclo*-C_6H_{10}; e: R=COPh; f: R=$COBu^t$; g: R=COPr.



Scheme 2. a: R=H; b: R=Bu; h: R=$C(OH)Me_2$; i: R=$CH(OH)(CH_2)_2Me$; j: R=$CH(OH)CHMe_2$.

depending on the structure of the alkynyl group. It was established that, in most cases, ketones are derived from dichlorides that are prone to rapid hydrolysis.

Our understanding of the heterocyclization of 2-alkynylanthraquinone-1-diazonium chlorides **3** was a starting point for the search of a route leading not only to a 5-membered heterocycle but also to the 6-membered pyridazine. We thought this might be achieved by using another acid instead of HCl with similar acidic properties but with low nucleophilic strength of the anion. Such requirements can be satisfied, for example, by sulfuric acid, in which the role of nucleophilic agent will be played by the H_2O molecule. It was assumed that this replacement of the nucleophilic agent would decrease the reaction rate. At the same time, we hoped that exclusion of the strong nucleophile would allow further transformations of the intermediate to isomerization into a 6-membered heterocycle. Indeed, when studying heterocyclization of a whole series of alkynylanthraquinonediazonium salts **7** in sulfuric acid, we observed a decrease of reaction rate and formation of naphthocinnolinetriones **9** (Scheme 2).

We studied this reaction in detail for **2a** as an example. It was found in the very first experiment involving the dilution of diazonium salt with water that a mixture of **6a** and **9a** is formed as the reaction products. The ^1H NMR spectrum of this mixture exhibits two signals corresponding to the NH of pyridazine (δ 13.77 ppm) and pyrazole (δ 12.34 ppm) rings. Exactly corresponding to the intensities of these signals are the signals from CH (δ 8.01 ppm) of the pyridazine in **9a** and CHO (δ 10.36 ppm) of the aldehyde group in **6a**. The ratio of cyclization products **6a** and **9a** was found to be strongly dependent on the acidity of solution used to dilute the diazonium salt. Table 1 shows the changes of this ratio depending on the concentration of sulfuric acid at the stage

Table 1. The dependence of the **9a**:**6a** ratio on the concentration of sulfuric acid

Dilution method	Concentration of H_2SO_4 (%)	Ratio **9a**:**6a**	Yield (%) (**9a**+**6a**)
A	0.4	1:3	79.6
B	1.6	2:1	92.2
C	16.1	4:1	90.0
D	38	16:1	90.4

Table 2. Characterization of 1*H*-naphtho[2,3-*h*]cinnoline-4,7,12-triones **9**

Compound	Yield (%)	Mp (°C) (toluene–hexane)	Formula	Found (Requires) (%)			Spectrum ^{1}H NMR, δ (ppm) ($CDCl_3$)	IR spectrum, ν (cm^{-1}) ($CDCl_3$)
				C	H	N		
9a	90.4	290–292	$C_{16}H_8N_2O_3$	69.76 (69.56)	2.97 (2.92)	10.13 (10.14)	7.81–7.97 m (2H, $H^{9,10}$), 8.01 s (1H, H^3), 8.24–8.45 m (2H, $H^{8,11}$), 8.25 d (1H, $H^{5(6)}$, J=8.4 Hz), 8.70 d (1H, $H^{6(5)}$, J=8.4 Hz), 13.77 br. s (1H, NH)	1650, 1680 (C=O), 3315 (NH)
9b	71.2	198–200	$C_{20}H_{16}N_2O_3$	72.30 (72.28)	4.77 (4.85)	8.50 (8.43)	0.97 t (3H, CH_3, J=7.3 Hz), 1.38–1.81 m (4H, $(CH_2)_2CH_3$), 2.87 t (2H, $CH_2(CH_2)_2CH_3$, J=7.3 Hz), 7.71–7.93 m (2H, $H^{9,10}$), 8.22 d (1H, $H^{5(6)}$, J=8.4 Hz), 8.26–8.40 m (2H, $H^{8,11}$), 8.70 d (1H, $H^{6(5)}$, J=8.4 Hz), 13.53 br. s (1H, NH)	1635, 1660, 1685 (C=O), 3320 (NH)
9h	91.0	209–211	$C_{19}H_{14}N_2O_4$	68.18 (68.26)	4.50 (4.22)	8.62 (8.38)	1.70 s (6H, CH_3), 7.80–7.97 m (2H, $H^{9,10}$), 8.28 d (1H, $H^{5(6)}$, J=8.3 Hz), 8.24–8.42 m (2H, $H^{8,11}$), 8.73 d (1H, $H^{6(5)}$, J=8.3 Hz), 13.70 br. s (1H, NH)	1660, 1690 (C=O), 3315 (NH)
9i	82.5	207–208.5	$C_{20}H_{16}N_2O_4$	69.00 (68.96)	4.84 (4.63)	7.99 (8.04)	0.98 t (3H, CH_3, J=7.3 Hz), 1.40–2.10 m (5H, CH_2—CH_2, OH), 4.96 m (1H, OCH), 7.82–7.97 m (2H, $H^{9,10}$), 8.27 d (1H, $H^{5(6)}$, J=8.4 Hz), 8.27–8.44 m (2H, $H^{8,11}$), 8.71 d (1H, $H^{6(5)}$, J=8.4 Hz), 13.73 br. s (1H, NH)	1630, 1655, 1680 (C=O), 3310 (NH)
9j	75.0	227–228.5	$C_{20}H_{16}N_2O_4$	68.85 (68.96)	4.59 (4.63)	7.96 (8.04)	0.99 d and 1.01 d (6H, CH_3, J=6.7 Hz), 2.36 m (1H, $CH(CH_3)_2$), 2.77 br. s (1H, OH), 4.69 d (1H, OCH, J=6.0 Hz), 7.68–8.09 m (2H, $H^{9,10}$), 8.27 d (1H, $H^{5(6)}$, J=8.4 Hz), 8.16–8.56 m (2H, $H^{8,11}$), 8.69 d (1H, $H^{6(5)}$, J=8.4 Hz), 13.74 br. s (1H, NH)	1635, 1660, 1685 (C=O), 3315 (NH)

of diazonium salt cyclization. It is essential that the cyclization rate is the same in all cases. This fact confirms the assumption that sulfuric acid does not participate in the first stage of cyclization and the role of nucleophilic agent is played by the solvent molecule H_2O. One can see from Table 1 that for higher sulfuric acid concentrations the main product of the reaction becomes 1*H*-naphtho[2,3-*h*]cinnoline-4,7,12-trione **9a**.

We performed the heterocyclization in 38% sulfuric acid of several other aminoalkynylanthraquinones **2b,h–j** that are known[1] to result in 1,1-dichloroalkyl-1*H*-naphtho[2,3-*g*]-indazole-6,11-diones in hydrochloric acid. In all the cases, the main reaction products were naphthocinnolines **9**. Table 2 shows the yields, physical characteristics and spectral properties of these compounds.

It should be noted that the enol intermediate **8** was never observed, which is quite reasonable. It undergoes further rapid transformations, either tautomerization into the more stable carbonyl form **6** or isomerization into a 6-membered heterocycle with the formation of **9**. The mechanism of the ring transformation will be the subject of a further investigation. It is already clear that this is an acid-catalyzed process.

Thus, a new view on the mechanism of heterocyclization of *ortho*-alkynylarenediazonium salts within the quinone series made it possible to govern the cyclization of these salts directing it to the formation of either a 5- or a 6-membered ring. This allowed us, starting from compounds **2**, to obtain both naphthoindazole and naphthocinnoline derivatives, the latter synthesized by this method for the first time.

3. Experimental

3.1. General

3.1.1. Cyclization of 1-amino-2-ethynyl-9,10-anthraquinone 2a. 38.0% H_2SO_4 (10 ml) and $NaNO_2$ (0.8 g, 1.2 mmol) in H_2O (1 ml) were added successively to **2a** (0.10 g, 0.4 mmol) in acetone (25 ml). The mixture was stirred for 1 min, and then the process of cyclization was performed in four variants, i.e. the solution of formed diazo salt was poured out into:

(A) 2.0% Na_2CO_3 solution (220 ml);
(B) H_2O (300 ml);
(C) 13.5% H_2SO_4 (100 ml);
(D) 38.0% H_2SO_4 (100 ml).

In each case, the aqueous solution, after extracting neutral components into $CHCl_3$, was stirred for 30 min at 65°C. Cyclization products were extracted with $CHCl_3$. The extract was thoroughly washed with water and dried. After evaporation of the solvent, the dry residue was analyzed for cyclization products **6a** and **9a** with the help of ^1H NMR spectra. The total yield of **6a** and **9a** was recorded after crystallization of the dry residue from a toluene–hexane mixture. The results are presented in Table 1.

Cyclization of other aminoalkynylanthraquinones **2b,h–j** was performed by variant D. The yields of the main products **9b,h–j** and their characteristics are presented in Table 2.

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