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IMPROVED METHOD FOR THE CYCLIZATION OF *ortho*-ALKYNYLBENZENEDIAZONIUM SALTS

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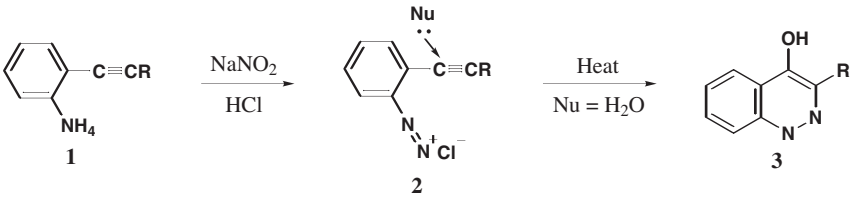
In the last decade, the Richter reaction has elicited considerable interest among chemists for two reasons: 1) the requirement to produce condensed heteroaromatic compounds with high biological activity, and 2) creation of convenient methods for introduction of alkyne groups into the aromatic ring, thereby making *vic*-alkynylaminoarenes accessible.[1] The cyclization of *ortho*-alkynylbenzenediazonium salts, discovered by Richter,[2] has been applied to the preparation of 4-hydroxycinnoline derivatives (*Eq. 1*).[3,4]

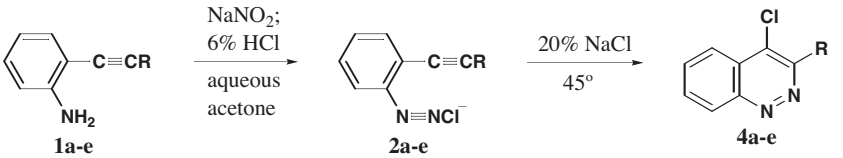


1 **2** **3** (1)

In the standard procedure, the conversion of anilines **1** into cinnolines **3** can be realized in a one-pot preparation. At the same time, the Richter reaction for the preparation of some cinnoline derivatives is limited because of its rigorous conditions. Acidity and high temperature lead to poor results in the conversion of *vic*-alkynylaminoarenes because of the concurrent hydrolysis of some functional groups. Transformation of the amino group (compound **1**) to the diazonium salt (compound **2**) enhances the reactivity of substituents; for example, all attempts to perform the cyclization of the 3-diethylamino-6-(heptyn-1-yl)-1,4-naphthoquinone-5-diazonium

chloride by the standard procedures were unsuccessful because of the hydrolysis of the diethylamino group.[5] As was shown recently,[6,7] the formation of 4-chlorocinnolines did not occur in the Richter reaction for the same reason. In the authors' opinion, the initial cyclic product, 4-chlorocinnoline, was hydrolyzed to the 4-hydroxycinnoline under these conditions. To obtain 4-chlorocinnolines, the authors carried out the cyclization at ambient temperature and reduced the reaction time. Apparently, due to the low conversion of the diazonium salts, the yields of the products under these conditions were only 11-45%.[6,7] The present paper describes an improved method of *ortho*-alkynylbenzenediazonium salt cyclization, which avoids side-reactions and leads to increased yields of the target products.

The changes in the procedure consist in the separation of the diazotization and cyclization steps. The diazotization of **1** is carried at low temperature (–10 to –5ºC) in an acetone-aqueous HCl solution, using an excess of $NaNO_2$ (up to 2-fold). Under such conditions, the process is complete within about 5 minutes, this step was monitored by TLC. After this, the cyclization of diazonium 2 can be carried out under rather mild conditions. Some of the principal features of this process have been investigated in the example of *ortho*-(phenylethynyl)benzenediazonium chloride **2a.** The most important aspect of this step is that the rate of reaction depends on the acidity of the solution. It is known that the acidity of the medium has a very strong influence on diazonium salt behavior.[8] It has been established that the cyclization rate does not depend on hydrogen-ion concentration and occurs without complications even in dilute acid. In neutral and alkaline media, the transformations of the diazonium salts are observed, but no cyclization. Another important characteristic is the dependence of cyclization efficiency on the nucleophilic properties of the medium. Intramolecular closure of the ring (*Eq. 1*) is accompanied by intermolecular interaction with the nucleophile. Formation of chlorocinnolines in this reaction demonstrates that chloride ion, as a strong nucleophile, participates in the reaction,[7] since the cyclization rate increases with increased chloride concentration, and, in 20% NaCl, is ten times faster than cyclization in water.



(2)

4a: R = Ph (75%)
4b: R = 4-NO_2Ph (85%)
4c: R = 3-NO_2Ph (83%)
4d: R = $C(CH_3)_2OH$ (67%)
4e: R = C_4H_9 (60%)

The optimum conditions for the cyclization are as follows: the solution of diazonium salt **2,** formed on the first step, was quickly diluted with ~15-fold 20% aqueous NaCl which resulted in decreased acidity. This led to an increase of the cyclization rate and a decrease of the

rate of side-reactions. Such an approach was successfully applied to obtain a series of 4-chlorocinnolines (*Eq. 2*) to obtain the materials in higher yields than previously reported.[7]

The ability to control the cyclization conditions allowed us to synthesize not only 4-chlorocinnolines, but also 4-bromocinnolines from diazonium chlorides **2**. As an example, it was shown that if cyclization of diazonium salt **2b** is performed in the presence of excess bromide anions, the reaction gives 4-bromo-3-(4-nitrophenyl)cinnoline in 90%. Moreover, this approach permits us to probe the reasons which prevent the formation of the cyclization product from 2-(4-dimethylaminophenylethynyl)aniline.[9] The absence of cyclization product is ascribed not to the efficiency of the cyclization step as was suggested earlier,[7] but rather to the diazotization step. By varying the conditions of the diazotization step, we obtained products of the cyclization in yields of ~80%. Contrary to the generally accepted view,[7,10,11] it was shown that cyclization of *ortho*-alkynylbenzenediazonium salts can result in the formation of indazole derivatives.[9] These results are not in agreement with the generally accepted one-stage mechanism of cyclization of *ortho*-alkynylbenzenediazonium salts proposed by Schofield and Simpson (Eq. 1, second step).[10,11] It is thus reasonable to reevaluate both the mechanism and synthetic potentials of this reaction. We hope that the new procedure will promote better use of the Richter reaction as a method of synthesis of potentially bioactive compounds.

EXPERIMENTAL SECTION

All ^{1}H NMR spectra were recorded using the Bruker DPX-200 spectrometer with Me_4Si as the internal standard. The chemical shifts and the coupling constants *J* are given in ppm (δ) and in Hz respectively. The reactions were monitored by TLC by using Silufol UV-254 plates (solvent: $CHCl_3$ -acetone 10:1).

The starting alkynylanilines **1a-e** were obtained by the cross-coupling of *ortho*-iodoanilines with the corresponding terminal acetylenes under copper-palladium catalysis.[12] The microanalytical and ^{1}H NMR data for the new *ortho*-alkynylanilines are given below.

1c: mp 105-106ºC (toluene-hexane). ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.30 (br.s, 2H, NH_2), 6.50-6.90 (m, 2H, H-4,6), 7.05-7.35 (m, 2H, H-3,5), 7.40-7.65 (m, 1H, H-5'), 7.75-7.92 (m, 1H, H-6'), 8.05-8.25 (m, 1H, H-4'), 8.30-8.50 (m, 1H, H-2').

Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.57; H, 4.24. Found: C, 70.55; H, 4.29.

1d: mp 65-66ºC (toluene-hexane).^{1}H NMR: δ 1.64 (s, 6H, $2CH_3$), 4.16 (br.s, 2H, NH_2), 6.60-6.80 (m, 2H), 7.05-7.20 (m, 1H, H-5), 7.25 (d, J = 6.8 Hz, 1H, H-3).

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.57; H 7.77; N, 7.87.

Cyclization of *ortho*-Alkynylanilines 1a-e into the Chlorocinnolines 4a-e; Representative Procedure.- The *ortho*-alkynylaniline **1** (0.42 mmol), 2 mL of 18% hydrochloric acid, 4 mL of acetone and 43.5 mg (0.63 mmol) of $NaNO_2$ was stirred at –10 to –5ºC. In 5 minutes, the diazonium salt **2** solution thus formed was diluted by 15-fold volume of the 20% NaCl aqueous solution, then maintained at 45ºC until completion of precipitation (the cyclization time was 60-90 min). The

precipitate was collected, washed with water, dried, and recrystallized from a 1:1 toluene-hexane mixture. The yields of the chlorocinnolines **4** amounted to 60-85% (Eq. 2).

Microanalytical and ^{1}H NMR data for the new 4-halogenocinnolines **4b-e** are given below.

4a: mp 118-119ºC (toluene-hexane), *lit*.[7] mp 118-119ºC.

4b: mp 221-222ºC (toluene-hexane), *lit*.[7] mp 178-179ºC. Compound **4b** has been completely re-characterized; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.92-8.03 (m, 2H, H-6,7), 8.13 (d, 2H, H-2',6'), 8.31-8.37 (m, 1H, H-5), 8.43 (d, 2H, H-3',5'), 8.62-8.68 (m, 1H, H-8).

Anal. Calcd. for $C_{14}H_8ClN_3O_2$: C, 58.86; H, 2.82; Cl, 12.41. Found: C, 59.13; H, 2.91; Cl, 12.07.

4c: mp 205-206ºC (toluene-hexane). ^{1}H NMR: δ 7.77 (t, 1H, H-7), 7.93-8.02 (m, 2H, H-5,6), 8.26-8.43 (m, 3H, H-5¢,6¢,8), 8.82-8.87 (m, 1H, H-4¢), 8.85(s, 1H, H-2¢).

Anal. Calcd. for $C_{14}H_8ClN_3O_2$: C, 58.86; H, 2.82; Cl, 12.41. Found: C, 59.05; H, 2.88; Cl, 12.28.

4d: mp 65-66ºC (toluene-hexane). ^{1}H NMR: δ 1.85 (s, 6H, $C(CH_3)_2$), 6.30 (s, 1H, OH), 7,80-8.0 (m, 2H, H-6,7), 8.20-8.40 (m, 1H, H-5), 8.50-8.70 (m, 1H, H-8).

Anal. Calcd. for $C_{11}H_{11}ClN_2O$: C, 59.33; H, 4.98; Cl, 15.92. Found: C, 59.20; H, 5.08; Cl, 15.83.

4e: mp 28-29ºC (toluene-hexane). ^{1}H NMR:δ 0.98 (t, 3H, CH_3), 1.48 (sextet, $J_{H,H}$ = 7.5 Hz, 2H, γ-CH_2), 1.88 (qu, $J_{H,H}$ = 7.5 Hz, 2H, b-CH_2,), 3.38 (t, $J_{H,H}$ = 7.5 Hz, 2H, α-CH_2,), 7.75-7.85 (m, 2H, H-6,7), 8.10-8.20 (m, 1H, H-5), 8.45-8.55 (m, 1H, H-8).

Anal. Calcd. for $C_{12}H_{13}ClN_2$: C, 65.31; H, 5.94; Cl, 16.06. Found: C, 65.29; H, 5.93; Cl, 16.17.

Cyclization of the *ortho*-**Alkynylaniline 1b into the Bromocinnoline**.- The diazonium salt **2b** generated as above was diluted with 15-fold volume of 20% KBr aqueous solution. In this case, the cyclization time was 20 min. The precipitate formed was processed in the same way as above. The yield of the bromocinnoline amounted to 90%, mp 216-217ºC, *lit*.[7] mp 164-165ºC. This compound has been completely characterized; ^{1}H NMR: δ 7.92-8.03 (m, 2H, H-6,7), 8.07 (d, $J_{H,H}$ = 8.6 Hz, 2H, H-2',6'), 8.25-8.33 (m, 1H, H-5), 8.42 (d, $J_{H,H}$ = 8.6 Hz,2H, H-3',5'), 8.60-8.68 (m, 1H, H-8).

Anal. Calcd. for $C_{14}H_8BrN_3O_2$: C, 50.93; H, 2.44; Br, 24.20. Found: C, 50.75; H, 2.56; Br, 24.42.

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