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The Richter reaction of *ortho*-(alka-1,3-diynyl)aryldiazonium salts

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Abstract—The cyclisation of various *ortho*-buta-1,3-diynylaryldiazonium salts was studied and shown to depend on the reaction conditions and nature of the substituents on the benzene ring. The reaction leads to 4-chloro-3-ethynylcinnolines, and/or 3-ethynyl-4-hydroxycinnolines, the latter undergoing subsequent cyclisation to give furo[3,2-*c*]cinnolines.

The cinnoline ring system has received considerable attention in recent years because many biologically active compounds have this structural component.[1] For over a hundred years, numerous methods for the preparation of cinnolines have been developed,[2] and the very first synthesis, described by Richter,[3a] was via the cyclisation of *ortho*-ethynylaryldiazonium salts.

4-Hydroxycinnolines were obtained in the first Richter cyclisations.[3] Later it was shown that the reaction led to 4-halo-substituted cinnolines, and their subsequent hydrolysis gave 4-hydroxycinnolines or the tautomeric 4(1*H*)-cinnolinones.[4] Thus, cyclisation favouring a 6-*endo*-*dig* pathway resulted in the formation of a pyridazine ring, although some examples of five-membered ring formation have also been reported.[5]

Although the Richter reaction has been thoroughly investigated for monoacetylene derivatives of aryl- and heteroaryldiazonium salts,[2–5] only one example of cyclisation of an *ortho*-buta-1,3-diynylaryldiazonium salt has been reported,[4b] due to the poor availability of *ortho*-buta-1,3-diynylarylamines. For these substrates, diazotisation and subsequent cyclisation could possibly give a *one*-*pot* approach to 3-ethynyl-4-chlorocinnolines which are attractive precursors for various fused heterocycles.[6]

Recently, we developed a convenient method for the preparation of functionalised aryl(hetaryl)diacetylenes, including diacetylene derivatives of arylamines.[7] Using this procedure,[7c] a series of *ortho*-buta-1,3-diynylanilines were prepared to investigate the cyclisation of *ortho*-buta-1,3-diynylbenzenediazonium salts, and the results are reported herein.

Diacetylene derivatives of aniline **1b** and 4-bromoaniline **1d** were selected for initial study. Diazotisation of **1b** and **1d** under commonly used conditions[4b] (procedure A) afforded 4-chloro-3-(dec-1-ynyl)cinnoline (**3b**) and 6-bromo-4-chloro-3-(oct-1-ynyl)cinnoline (**3d**) in yields of 23% and 10%, respectively (Scheme 1, Table 1, entries 1 and 2). Small amounts of the reductive deamination products **5b** and **5d** were also isolated from the reaction mixtures. Under these conditions (procedure A), the reaction is a heterophasic process due to the low solubility of the starting diynylaniline hydrochlorides in aqueous medium and, accordingly, excessive resinification of the reaction mixture occurred.

We decided to modify the reaction conditions by using an organic diazotisation agent and by adding organic solvents to the mixture. Buta-1,3-diynylanilines **1a**,**b**,**d**–**f** were chosen for screening of the new reaction conditions. The use of butyl nitrite in the presence of a catalytic amount of sulfuric acid (procedure B, entry 3) did not improve the diazotisation protocol. The yields and ratios of the products were similar to those obtained in entry 1. The addition of THF (procedure C) also offered little advantage (cf. entries 2 and 4).

Procedure D, wherein diazotisation was carried out in the presence of a diethyl ether/hexane mixture, was

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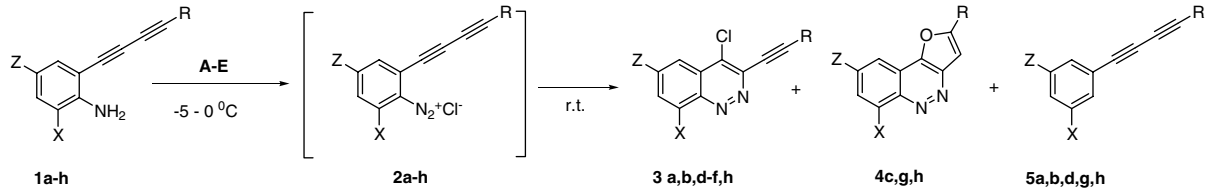

Scheme 1. Reagents and conditions: A: $NaNO_2$ (1.1 equiv), HCl (36%) 5 mL; B: BuONO (1.1 equiv), H_2SO_4 (concd); C: $NaNO_2$ (1.1 equiv), HCl (36%) 5 mL, THF; D: $NaNO_2$ (1.1 equiv), HCl (36%) 5 mL, Et_2O/hexane (1:1); E: $NaNO_2$ (1.1 equiv), MeOH saturated HCl gaseous.

Table 1. Diazotisation of diynylanilines **1**[8,9]

Entry	Diynylaniline	R	X	Z	Procedure	Products (yield, %)		
						3	**4**	**5**
1	**1b**	*n*-C_8H_{17}	H	H	**A**	**3b** (23%)		**5b** (7%)
2	**1d**	*n*-C_6H_{13}	H	Br	**A**	**3d** (10%)		**5d** (5%)
3	**1b**[a]	*n*-C_8H_{17}	H	H	**B**	**3b** (24%)		**5b** (5%)
4	**1d**	*n*-C_6H_{13}	H	Br	**C**	**3d** (12%)		**5d** (12%)
5	**1a**	*n*-C_6H_{13}	H	H	**D**	**3a** (54%)		**5a** (5%)
6	**1e**[a]	*n*-C_8H_{17}	H	Br	**D**	**3e** (27%)		
7	**1f**[a]	*n*-C_8H_{17}	Br	CH_3	**D**	**3f** (33%)		
8	**1g**	*n*-C_6H_{13}	H	NO_2	**D**		**4g** (47%)	**5g** (20%)
9	**1h**	*n*-C_8H_{17}	H	COOMe	**D**	**3h** (15%)	**4h** (27%)	
10	**1h**[a]	*n*-C_8H_{17}	H	COOMe	**D**	**3h** (14%)	**4h** (15%)	**5h** (13%)
11	**1c**[a]	*n*-$C_{10}H_{21}$	H	H	**E**		**4c** (39%)	
12	**1h**[a]	*n*-C_8H_{17}	H	COOMe	**E**		**4h** (54%)	**5h** (11%)

[a] The hydrochlorides of the starting amines were used.

found to be a more successful protocol, with increased yields of the target chlorocinnolines (entries 5–7). The addition of Et_2O assists the solubility of the starting material during diazotisation; subsequent addition of hexane at the cyclisation step, on the other hand, led to the formation of a biphasic system again with in situ removal of the products from the aqueous medium.

According to an earlier study, 4-hydroxycinnolines (4(1*H*)-cinnolinones) can be formed in the Richter reaction as the result of 4-chlorocinnolines hydrolysis.[4] However, no 4-hydroxycinnolines were detected in the reactions of the *ortho*-buta-1,3-diynylbenzenediazonium salts **1a**,**b**,**d**–**f** under our conditions (A–D).

Apparently, the nature of substituents on the benzene ring influences the formation of the hydroxycinnolines; this however, has not previously been studied in the context of the Richter reaction.

To gain a clearer view of the effect of substituents, we chose alka-1,3-diynylanilines **1g** and **1h**, which have electron withdrawing groups, and procedure D was used. Diazotisation of **1g**, containing a strongly electron withdrawing nitro group, led to the formation of furo[3,2-*c*]cinnoline **4g** in 47% yield, along with a considerable amount of the deamination product **5g** (entry 8). 1-(2-Chloro-4-nitrophenyl)deca-1,3-diyne, formed as a result of diazonium group substitution, was also isolated from the reaction mixture (9%). No trace of a 4-chlorocinnoline derivative was detected. The reaction of **1h** gave a mixture of 4-chlorocinnoline **3h** and furocinnoline **4h** (entry 9). When the reaction mixture was cooled during cyclisation to −13 °C, it gave rise to a competing deamination process (entry 10).

Evidently, the furocinnolines arose from the 4-hydroxycinnolines as a result of subsequent intramolecular addition of the hydroxyl group to the triple bond. In turn, the formation of hydroxycinnolines in the reactions of **1g**,**h** accords with the mechanism of 4-chlorocinnoline hydrolysis, that is an S_NAr process promoted by electron acceptor substituents.[10]

A surprising result was obtained when MeOH saturated with gaseous HCl was used as the solvent in the reaction of **1c** (procedure E, entry 11). TLC monitoring indicated that formation of the aryldiazonium salt was faster in comparison with previous procedures. After work-up, the only product obtained was the 2-decylfuro[3,2-*c*]cinnoline (**4c**) in a 39% yield. Similarly, diazotisation of **1h** in MeOH gave furo[3,2-*c*]cinnoline **4h** as the main product, along with the reductive deamination product **5h** (entry 12). The formation of furo[3,2-*c*]cinnolines has been reported earlier, in the Pd/Cu catalysed cross-coupling of 3-iodo-4(1*H*)-cinnolinone with terminal acetylenes.[7] Copper(I) iodide was supposed to be the catalyst for the subsequent cyclisation. In our case, diazotisation of *ortho*-buta-1,3-diynylanilines in methanol medium gives furo[3,2-*c*]cinnolines directly.

This study demonstrates features of the Richter reaction of *ortho*-buta-1,3-diynylaryldiazonium salts, which are dependent on the reaction conditions and the substituents on the benzene ring. Electron withdrawing substituents and MeOH as solvent were found to assist

furo[3,2-*c*]cinnoline formation via 3-ethynyl-4-hydroxycinnoline cyclisation.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.05.055.

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8. All compounds were characterised by NMR, MS, and CHN analysis, and yields refer to isolated products.
9. *A typical reaction procedure D is as follows*: concentrated HCl (10 mL) was added to a solution of amine **1h** (1 mmol) in diethyl ether (3 mL). The reaction mixture was cooled to −10 °C, and an aqueous solution of $NaNO_2$ (76 mg, 1.1 mmol in 2 mL H_2O) was added dropwise over 20 min to avoid heating the reaction mixture above 0 °C. After TLC showed complete conversion of starting material, the reaction mixture was stirred for a further 8–12 h at room temperature. The reaction mixture was poured into an aqueous solution of Na_2CO_3 which was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with saturated aqueous NH_4Cl solution (30 mL) and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified on silica gel using hexane/EtOAc (40:1) to afford **3h** (54 mg, 15%) and **4h** (92 mg, 27%). **3h**: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.90$ (t, $^3J_{H,H} = 6.5$ Hz, 3H, CH_3), 1.26–1.34 (m, 8H, 4^*CH_2); 1.54–1.63 (m, 2H, $C{\equiv}CCH_2CH_2CH_2$), 1.77 (tt, $^3J_{H,H} = {}^3J_{H,H} = 6.5$ Hz, 2H, $C{\equiv}CCH_2CH_2$), 2.66 (t, $^3J_{H,H} = 6.5$ Hz, 2H, $C{\equiv}CCH_2$), 4.06 (s, 3H, O–CH_3), 8.43 (dd, $^3J_{H,H} = 8.8$ Hz, $^4J_{H,H} = 2.0$ Hz, 1H, 7-H), 8.64 (d, $^3J_{H,H} = 8.8$ Hz, 1H, 8-H), 8.91 (d, $^3J_{H,H} = 2.0$ Hz, 1H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 14.5$, 20.3, 23.1, 28.6, 29.4, 29.5, 29.6, 32.2, 53.41, 66.3, 102.2, 124.2, 126.7, 130.8, 131.2, 133.7, 137.4, 142.0, 149.6, 165.8 ppm. MS (EI): m/z (100%) = 360 (5) [M+^{37}Cl], 358 (16) [M$^+$], 323 (100), 316 (17), 302 (25), 295 (20), 281 (88), 267 (59), 260 (41). Anal. Calcd for CHN, $C_{20}H_{23}N_2O_2Cl$ (358.9): C, 66.94; H, 6.46; N, 7.81. Found: C, 66.97; H, 6.41; N, 7.60. **4h**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.90$ (t, $^3J_{H,H} = 6.5$ Hz, 3H, CH_3), 1.31–1.83 (m, 10H, 5^*CH_2), 1.88 (tt, $^3J_{H,H} = {}^3J_{H,H} = 6.5$ Hz, 2H, CH_2), 2.98 (t, $^3J_{H,H} = 6.5$ Hz, 2H, CH_2), 4.07 (s, 3H, O–CH_3), 7.15 (s, 1H, 3-H), 8.36 (d, $^3J_{H,H} = 8.8$ Hz, 1H, 7-H), 8.70 (d, $^3J_{H,H} = 8.8$ Hz, 1H, 6-H), 9.01 (s, 1H, 9-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 14.5, 23.0, 27.9, 29.1, 29.5, 29.6, 29.7, 32.2, 53.2, 103.2, 113.6, 123.1, 128.2, 131.0, 132.2, 143.7, 148.1, 148.5, 164.2, 166.2 ppm. MS (EI): m/z (*100%*) = 340 (22) [M$^+$], 297 (34), 269 (15), 242 (100), 218 (21). Anal. Calcd for CHN, $C_{20}H_{24}N_2O_3$ (340.4): C, 70.56; H, 7.11; N 8.23. Found: C, 70.35; H, 7.05; N, 7.94.
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