

A directive effect of heterofunctions in cyclocondensation reactions of acetylenylquinones with hydrazine

Igor I. Barabanov, Irina D. Ivanchikova and Mark S. Shvartsberg*

Institute of Chemical Kinetics and Combustion, Siberian Branch of the Russian Academy of Sciences, 630090 Novosibirsk, Russian Federation. Fax: +7 3832 34 2350; e-mail: shvarts@kinetics.nsc.ru

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The heterocycle formed in the cyclocondensation reactions of 2-acetylenyl-1-chloro-9,10-anthraquinones or 5-acetylenyl-3-diethylamino-1,4-naphthoquinones with NH_2NH_2 is influenced by the presence of a heterofunction, *e.g.* a hydroxyl group, in the acetylenic substituent; this directive effect was used for the synthesis of naphtho[2,3-*h*]cinnoline-4,7,12-trione and 4*H*-naphtho[1,8-*cd*]-1,2-diazepin-8-one derivatives.

Acetylenic derivatives of cinnoline and benzene with a labile chlorine atom at the *ortho* position react with hydrazine to close a pyrazole ring.^{1–3} When continuing our studies of the heterocyclization of acetylenylquinones,^{4,9} we carried out this condensation in the anthraquinone series.

In 2-acetylenyl-1-chloro-9,10-anthraquinones **1**, the halogen atom is readily substituted by nucleophilic groups,¹⁰ and the triple bond activated by the quinone nucleus is efficiently attacked by N-nucleophiles.¹¹ This attack is directed onto the β -C atom of the triple bond. Therefore, we supposed that the cyclocondensation of **1** with NH_2NH_2 will result in the formation of a six-membered diazine ring rather than a five-membered diazole ring as in the above reactions.^{1–3} In addition, competitive heterocyclization with the participation of the *peri*-carbonyl group can play a noticeable role.

We found that anthraquinones **1** easily condense with NH_2NH_2 (pyridine, 90–115 °C). Compounds **1a,b** with no heteroatomic groups in their acetylenic substituents are transformed to only pyrazole derivatives. Compound **1a** gives a mixture of 3-phenylethynyl-dibenzo[*cd,g*]indazol-6-one **2a**[†] and 3-benzyl-naphtho[2,3-*g*]indazole-6,11-dione **3a**[†] (~2:1) in 66% yield. The main product obtained from **1b** is pyrazoloanthrone **2b**[†] (45% yield).

However, the reaction route is changed when starting quinone **1** has a hydroxyl group at the γ -C atom of its side chain. The

condensation product of **1c** was found to be 1,2-dihydro-3-(1-hydroxy-1-methylethyl)naphtho[2,3-*h*]cinnoline-7,12-dione **4c**. This compound is reactive and can undergo transformations in the course of its isolation and purification.

We found that H_2O_2 readily oxidises **4c** to naphthocinnoline-trione **5c** (possibly, *via* the tautomeric 4*H*-form) and developed the one-pot synthesis of **5c** starting from **1c** (85% yield). This procedure was applied to the heterocyclization of ether **1d** and alcohols **1e,f**. The formation of **4d–f** was monitored by TLC. The routes of reactions are the same as for **1c** and lead to anthraquinones fused with a pyridazine ring **5d–f**.[†]

Thus, heterofunctions (a hydroxyl or alkoxy group) at the γ -C atom of the acetylenic substituents facilitate the participation of the triple bond in the formation of a heterocycle and the attack on the β -C atom of this substituent by the nucleophile.

A similar specific effect of heterofunctions has been observed in another reaction, the cyclocondensation of *peri*-acetylenylquinones with NH_2NH_2 .

Recently, we reported the cyclocondensation of 3-diethylamino-5-phenylethynyl-1,4-naphthoquinone **6a** with hydrazine.⁹ This reaction results in the closure of a six-membered pyridazine ring and affords **7a**. Unlike **6a**, *peri*-acetylenyl-9,10-anthraquinones with NH_2NH_2 form a seven-membered diazepine ring to give 4*H*-naphtho[9,1-*cd*]-1,2-diazepin-8-ones **8**.⁴

To prepare previously unknown interesting heterocyclic system of 4*H*-naphtho[1,8-*cd*]-1,2-diazepin-8-one, we attempted to change the direction of the cyclocondensation of 5-acetylenyl-3-diethylamino-1,4-naphthoquinones **6** with the use of orienting heterofunctions. Quinones **6b–d** (hydroxyacetylenyl analogues

[†] All new compounds gave satisfactory microanalytical and spectroscopic data.

2a: mp 281–283 °C. ¹H NMR (250 MHz, CDCl_3) δ : 7.40–7.50 (m, 3H, Ph), 7.50–7.75 (m, 4H, Ph, $\text{H}^{8,9}$), 7.80 (d, 1H, $\text{H}^{4(5)}$, J 7.5 Hz), 8.05 (d, 1H, $\text{H}^{5(4)}$, J 7.5 Hz), 8.27 (d, 1H, $\text{H}^{7(10)}$, J 7.6 Hz), 8.46 (d, 2H, $\text{H}^{10(7)}$, J 8.1 Hz).

2b: mp 170.5–171 °C. ¹H NMR (250 MHz, CDCl_3) δ : 0.90 (t, 3H, Me, J 6.8 Hz), 1.20–1.55 (m, 4H, MeCH_2CH_2), 1.60–1.75 (m, 2H, $\text{CH}_2\text{CH}_2\text{C}\equiv$), 2.52 (t, 2H, $\text{CH}_2\text{C}\equiv$, J 7.0 Hz), 7.59 (d, 1H, $\text{H}^{4(5)}$, J 7.4 Hz), 7.50–7.80 (m, 2H, $\text{H}^{8,9}$), 7.98 (d, 1H, $\text{H}^{5(4)}$, J 7.4 Hz), 8.26 (d, 1H, $\text{H}^{7(10)}$, J 7.2 Hz), 8.48 (d, 1H, $\text{H}^{10(7)}$, J 8.1 Hz).

3a: mp 224–225 °C. ¹H NMR (250 MHz, CDCl_3) δ : 4.41 (s, 2H, CH_2), 7.30–7.35 (m, 5H, Ph), 7.75–7.85 (m, 2H, $\text{H}^{8,9}$), 7.86 (d, 1H, $\text{H}^{4(5)}$, J 8.6 Hz), 7.97 (d, 1H, $\text{H}^{5(4)}$, J 8.6 Hz), 8.25–8.40 (m, 2H, $\text{H}^{7(10)}$), 11.70 (br. s, 1H, NH).

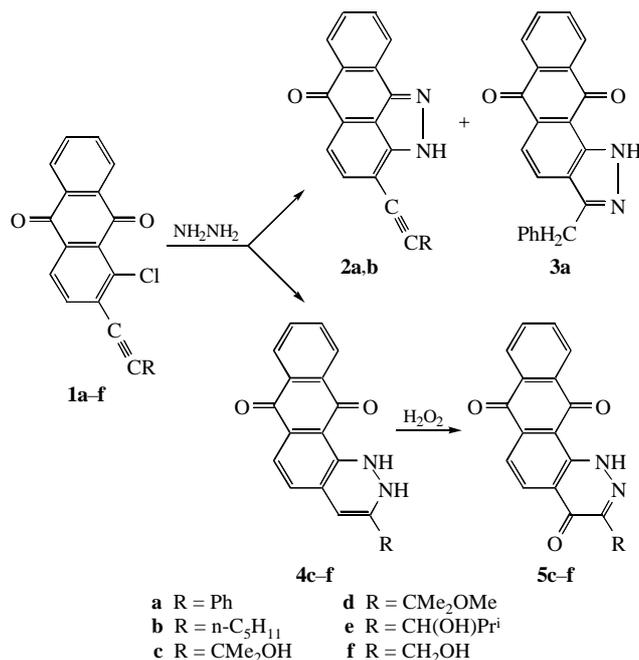
4c: mp 216.5–218.5 °C. ¹H NMR (250 MHz, CDCl_3) δ : 1.83 (s, 6H, Me), 7.80–7.95 (m, 3H, $\text{H}^{5(6),9,10}$), 8.12 (s, 1H, H^4), 8.22 (d, 1H, $\text{NH}^{(2)}$, J 8.6 Hz), 8.25–8.45 (m, 3H, $\text{H}^{6(5),8,11}$), 8.65 (d, 1H, $\text{NH}^{(2)}$, J 8.6 Hz).

5c: yield 85.2%, mp 209–211 °C. ¹H NMR (250 MHz, CDCl_3) δ : 1.70 (s, 6H, Me), 7.80–7.95 (m, 2H, $\text{H}^{9,10}$), 8.28 (d, 1H, $\text{H}^{5(6)}$, J 8.3 Hz), 8.25–8.40 (m, 2H, $\text{H}^{8,11}$), 8.73 (d, 1H, $\text{H}^{6(5)}$, J 8.3 Hz), 13.70 (br. s, 1H, NH).

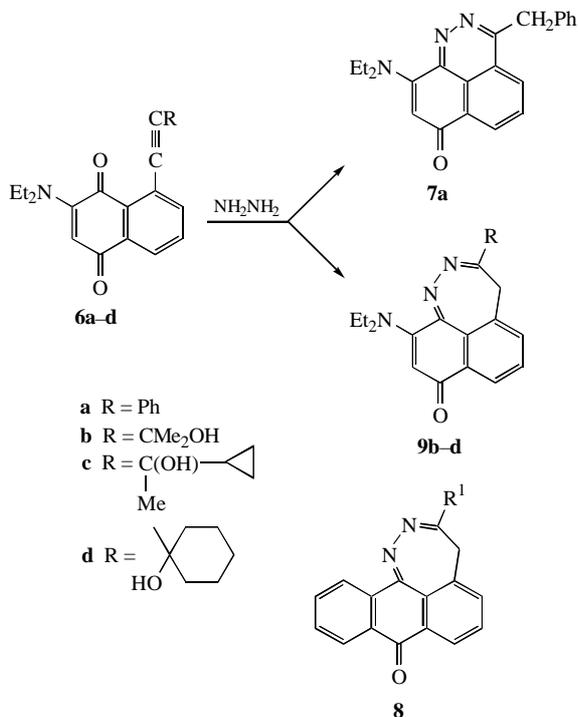
5d: yield 53.5%, mp 224–226 °C. ¹H NMR (250 MHz, CDCl_3) δ : 1.72 (s, 6H, Me), 3.30 (s, 3H, OMe), 7.75–7.95 (m, 2H, $\text{H}^{9,10}$), 8.24 (d, 1H, $\text{H}^{5(6)}$, J 8.3 Hz), 8.15–8.40 (m, 2H, $\text{H}^{8,11}$), 8.71 (d, 1H, $\text{H}^{6(5)}$, J 8.3 Hz), 13.61 (br. s, 1H, NH).

5e: yield 46.7%, mp 227–228.5 °C. ¹H NMR (250 MHz, CDCl_3) δ : 0.99 (d, 3H, Me, J 6.7 Hz), 1.01 (d, 3H, Me, J 6.7 Hz), 2.36 (m, 1H, CHMe_2), 2.77 (br. s, 1H, OH), 4.69 (d, 1H, OCH, J 6.0 Hz), 7.70–8.10 (m, 2H, $\text{H}^{9,10}$), 8.27 (d, 1H, $\text{H}^{5(6)}$, J 8.4 Hz), 8.15–8.55 (m, 2H, $\text{H}^{8,11}$), 8.69 (d, 1H, $\text{H}^{6(5)}$, J 8.4 Hz), 13.74 (br. s, 1H, NH).

5f: yield 38.8%, mp >275 °C (decomp.). ¹H NMR (250 MHz, CDCl_3) δ : 4.88 (s, 2H, CH_2), 7.85–7.95 (m, 2H, $\text{H}^{9,10}$), 8.29 (d, 1H, $\text{H}^{5(6)}$, J 8.4 Hz), 8.25–8.40 (m, 2H, $\text{H}^{8,11}$), 8.72 (d, 1H, $\text{H}^{6(5)}$, J 8.4 Hz), 13.78 (br. s, 1H, NH).



Scheme 1



Scheme 2

of **6a**) were condensed with NH_2NH_2 under the same conditions as in the cyclization of **6a** (pyridine, 115°C). Hydroxyacetylenylquinones **6b-d** were found to yield 3-substituted naphthodiazepinones **9b-d**.[‡] The reaction was accompanied by the formation of by-products and resins. Nevertheless, the yields of purified **9b-d** were 53–56%.

[‡] **9b**: mp $88\text{--}89^\circ\text{C}$. $^1\text{H NMR}$ (200 MHz, CDCl_3) δ : 1.28 (t, 6H, MeCH_2 , J 7.0 Hz), 1.43 (s, 3H, Me), 1.55 (s, 3H, Me), 2.78 (d, 1H, H_a^4 , J 12.7 Hz), 3.91 (d, 1H, H_b^4 , J 12.7 Hz), 3.45–3.65 (m, 4H, NCH_2), 3.85 (br. s, 1H, OH), 5.69 (s, 1H, H^9), 7.32 (d, 1H, H^5 , J 7.6 Hz), 7.56 (t, 1H, H^6 , J 7.6 Hz), 7.92 (d, 1H, H^7 , J 7.6 Hz).

9c: mp $156\text{--}157^\circ\text{C}$ (a mixture of diastereomers). $^1\text{H NMR}$ (200 MHz, CDCl_3) δ : $-0.20\text{--}0.15$, $0.30\text{--}0.70$ and $0.80\text{--}1.00$ (3m, 5H, cyclopropyl), 1.20–1.40 and 1.54 (m and s, 9H, MeCH_2 , MeCOH), 2.90 (d, 1H, H_a^4 , J 12.6 Hz), 3.91 (d, 1H, H_b^4 , J 12.6 Hz), 3.45–3.65 (m, 4H, NCH_2), 3.73 (br. s, 1H, OH), 5.74 (s, 1H, H^9), 7.31 and 7.35 (2d, 1H, H^5), 7.58 and 7.62 (2t, 1H, H^6), 8.03 and 8.06 (2d, 1H, H^7).

9d: mp $123\text{--}125^\circ\text{C}$. $^1\text{H NMR}$ (200 MHz, CDCl_3) δ : 1.29 (t, 6H, Me, J 7.0 Hz), 1.40–2.00 (m, 10H, cyclohexyl), 2.73 (d, 1H, H_a^4 , J 12.7 Hz), 3.95 (d, 1H, H_b^4 , J 12.7 Hz), 3.30 (br. s, 1H, OH), 3.40–3.65 (m, 4H, NCH_2), 5.72 (s, 1H, H^9), 7.35 (d, 1H, H^5 , J 7.5 Hz), 7.59 (t, 1H, H^6 , J 7.5 Hz), 8.00 (d, 1H, H^7 , J 7.5 Hz).

Thus, in the cyclocondensation of *peri*-acetylenyl-1,4-naphthoquinones **6** as well as in the above reaction of 2-acetylenyl-1-chloro-9,10-anthraquinones **1** with NH_2NH_2 , the hydroxyl group of a substituent directs the attack of the N-nucleophile onto the β -C of this substituent.

It is well known that the regio- or stereoselectivity of reactions such as the lithiation of aromatic compounds and the epoxidation of allyl alcohols is determined by the association of a substrate with a reagent.^{12,13}

We suppose that the directive effect of heterofunctions in the hydrazine cyclocondensations also belongs to this range of phenomena and can be explained by the association of the function with NH_2NH_2 by hydrogen bonds.

Note that the reactions considered offer ways for the synthesis of new condensed heterocyclic systems.

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