Acetylenic compounds as key intermediates in heterocyclic synthesis: a route to functionalized naphtho[2,3-*h*]quinoline-7,12-diones

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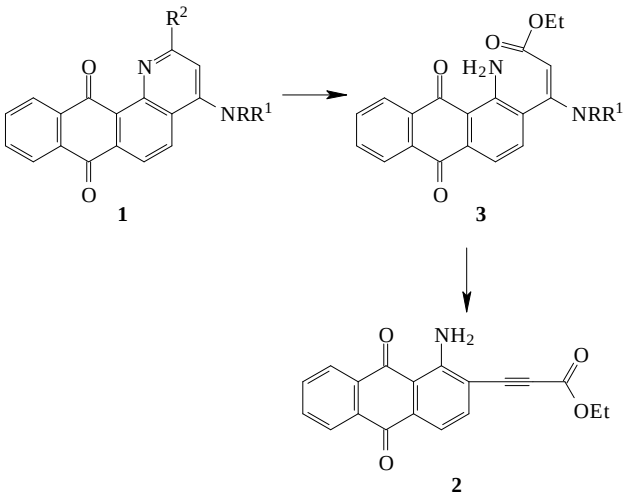
Addition of primary and secondary amines to ethyl (1-amino-9,10-anthraquinon-2-yl)propiolate and cyclization of the resulting adducts to 2-substituted 4-dialkyl(or alkyl)aminonaphtho[2,3-*h*]quinoline-7,12-diones and 4-dialkyl(or alkyl)amino-1,2-dihydronaphtho[2,3-*h*]quinoline-2,7,12-triones are reported.

A variety of biologically active and other potentially useful compounds include the quinoline nucleus.[1,2] For the last two decades heteroannulation processes based on transition metal catalysed reactions have been applied to the synthesis of quinolines.[3–5] One of the variants of this methodology involves *vic*-acetylenylaminoaromatic compounds as key intermediates which are prepared by Pd- or/and Cu-catalysed cross-coupling of the respective *ortho*-iodoanilines with terminal acetylenes.[6–10]

In this paper we report a route to the synthesis of hitherto unknown 2-functionalized 4-dialkyl(or alkyl)aminonaphtho-[2,3-*h*]quinoline-7,12-diones **1** using ethyl (1-amino-9,10-anthraquinon-2-yl)propiolate **2** as the key intermediate. The general plan of the synthesis is represented below (Scheme 1).



Scheme 1

Acetylenic quinones appertain to a specific group of acetylenic derivatives. In this work some points concerning the regio- and stereoselectivity of nucleophilic addition of amines to the triple bond of the ester **2** have been revealed, conditions for cyclizing the adducts have been determined and a simple procedure for the direct cross-coupling of 1-amino-2-iodo-9,10-anthraquinone **4** with ethyl propiolate **5** has been developed.

The Pd-catalysed cross-coupling reaction of aromatic halides with terminal acetylenes[11] appeared to be an effective method of preparing the key intermediate **2**. However, it is known that this condensation with the acetylenic ester **5** under normal conditions fails to yield cross-coupling products.[12] Taking into account the heightened reactivity of 2-iodo-9,10-anthraquinones and the sensitivity of **5** towards amines we replaced Et_3N commonly used as a base and a solvent in this reaction by an aqueous solution of K_2CO_3 and dioxane. Under the modified conditions **4** readily reacted with **5** to give **2**[†] in 74% yield (Scheme 2).

To form the appropriately-substituted pyridine ring, amines **6a**–**c** were added to acetylenic ester **2** (dioxane, 80 °C, 4–16 h). The acetylene **2** contains two substituents activating the triple bond – the ethoxycarbonyl group and the anthraquinone nucleus, which orient the nucleophile to different carbon atoms. Indeed, two types of compounds, adducts **3a**–**c** as the main products (yields 60–66%) and 3-aminonaphthoquinolones **8a**–**c** (yields 12–18%), the latter obviously due to the lactanization of the regioisomeric adducts **7a**–**c**, were formed.[‡] Compounds **3** and **8** were easily separated by column chromatography on Al_2O_3.

It was found that **3a**–**c** could be cyclized into 2-chloronaphtho-quinolines **9a**–**c** (yields 40–67%) upon heating with $POCl_3$ in dioxane for 1.5–5.5 h at 80 °C (method A). Also **3a**–**c** undergo base-catalysed cyclization (KOH, dibenzo[18]-crown-6, benzene, 20 °C) to aminolactams **10a**–**c** in 52–97% yields (method B). In their turn, lactams **10** can be readily transformed into chloroquinolines **9** by heating with $POCl_3$ in dioxane, as shown for **10a** (yield of **9a** 67%). Continuous refluxing of **10b** with $HC(OEt)_3$ in the presence of H_2SO_4 in benzene leads to 2-ethoxyquinoline **11b** in 54% yield. A mixture of the corresponding quinolone **10a**,**b** and 2-ethoxyquinoline **11a**,**b** in the ratio of ~2 : 1 can be obtained in 90% yield by acid-catalysed cyclization of **3a**,**b** in benzene at 20 °C (method C).

The ability of adducts **3** and **7** to undergo cyclization under mild conditions apparently implies the *syn*-addition of amines **6** to the triple bond of **2**.

Nucleophilic substitution of the labile chlorine atom in naphthoquinolines **9** is a route to various 2-substituted 4-dialkyl(or alkyl)aminonaphtho[2,3-*h*]quinoline-7,12-diones. For example, compounds **12**–**14** were prepared in 56–83% yields

† All new compounds gave satisfactory microanalytical and spectroscopic data. For **2**: mp 179–180 °C (from benzene–hexane); ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.38 (t, 3H, *J* 7.7 Hz, CH_3), 4.32 (q, 2H, *J* 7.7 Hz, CH_2), 7.52 (d, 1H, *J* 9.2 Hz, $H^{3(4)}$), 7.73 (d, 1H, *J* 9.2 Hz, $H^{4(3)}$), 7.70–7.95 (m, 2H, $H^{6,7}$), 8.15–8.40 (m, 2H, $H^{5,8}$); IR ($CHCl_3$) ν_{max}/cm^{-1} 1650, 1680 (C=O), 1715 (COOEt), 2220 (C≡C), 3340, 3495 (NH_2).

‡ Examples of typical ^{1}H NMR spectra for **3** and **8**–**11** are given below.

For **3a**: (90 MHz, $CDCl_3$) δ 0.85–1.25 (m, 9H, CH_3), 2.95–3.40 (m, 4H, NCH_2), 3.89 (q, 2H, *J* 7.7 Hz, OCH_2), 4.90 (s, 1H, =CH), 7.02 (br. s, 2H, NH_2), 7.27 (d, 1H, *J* 8.3 Hz, $H^{3(4)}$), 7.69 (d, 1H, *J* 8.3 Hz, $H^{4(3)}$), 7.60–7.85 (m, 2H, $H^{6,7}$), 8.10–8.40 (m, 2H, $H^{5,8}$).

For **8a**: 1.27 (t, 6H, *J* 7.7 Hz, CH_3), 3.60 (q, 4H, *J* 7.7 Hz, CH_2), 6.62 (s, 1H, H^4), 7.62 (d, 1H, *J* 9.3 Hz, $H^{5(6)}$), 7.98 (d, 1H, *J* 9.3 Hz, $H^{6(5)}$), 7.65–7.90 (m, 2H, $H^{9,10}$), 8.15–8.40 (m, 2H, $H^{8,11}$), 12.67 (br. s, 1H, NH).

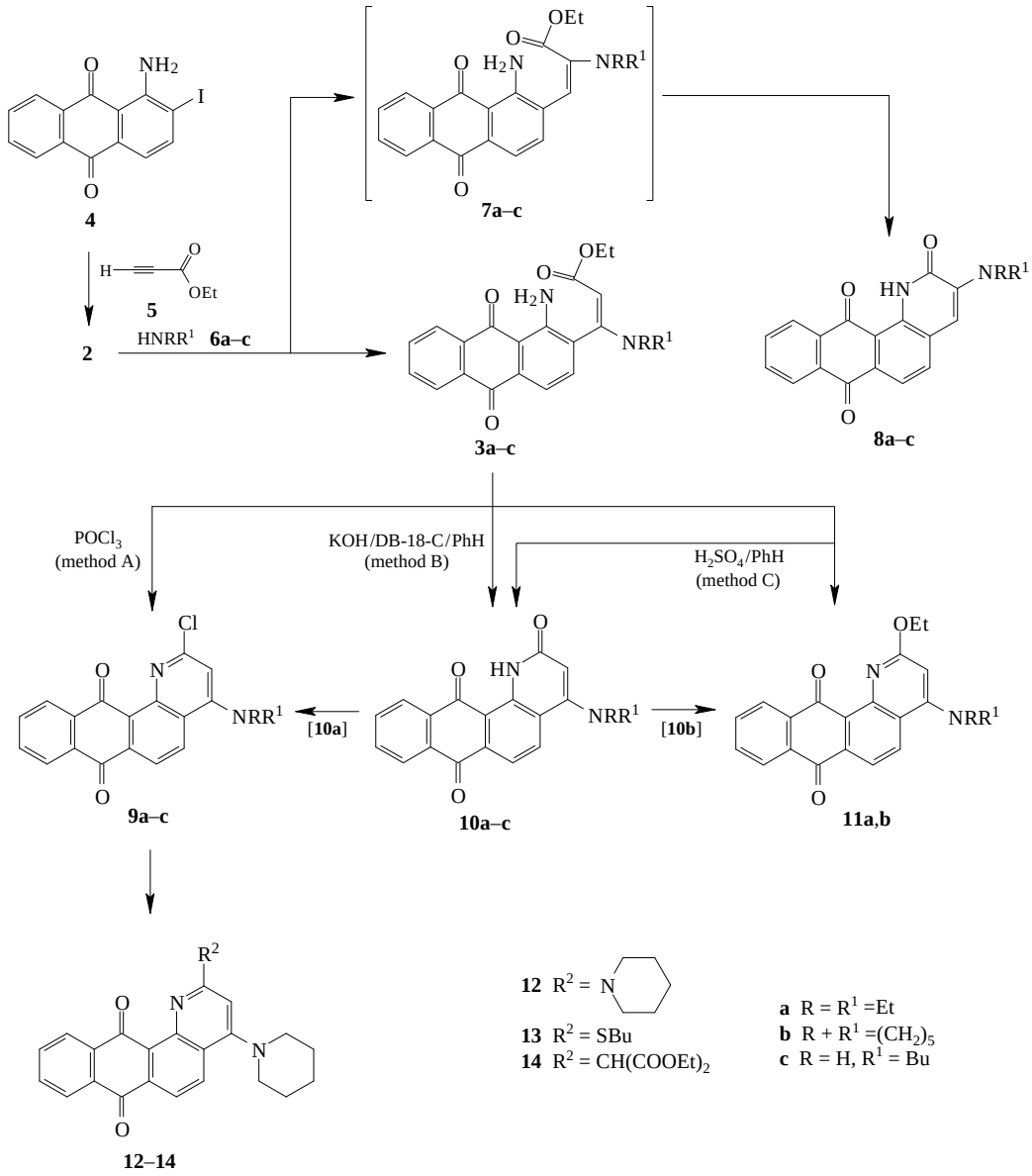
For **9a**: 1.13 (t, 6H, *J* 7.7 Hz, CH_3), 3.32 (q, 4H, *J* 7.7 Hz, CH_2), 6.82 (s, 1H, H^3), 7.55–7.80 (m, 2H, $H^{9,10}$), 8.00–8.35 (m, 4H, $H^{5,6,8,11}$).

For **9b**: 1.60–2.10 [m, 6H, $-(CH_2)_3-$], 3.10–3.45 (m, 4H, CH_2NCH_2), 6.93 (s, 1H, H^3), 7.65–7.95 (m, 2H, $H^{9,10}$), 8.15–8.45 (m, 4H, $H^{5,6,8,11}$).

For **9c**: 0.97 (t, 3H, *J* 7.6 Hz, CH_3), 1.20–1.95 (m, 4H, CH_2CH_2), 3.10–3.40 (m, 2H, NCH_2), 5.40 (br. m, 1H, NH), 6.45 (s, 1H, H^3), 7.60–7.90 (m, 2H, $H^{9,10}$), 7.95–8.35 (m, 4H, $H^{5,6,8,11}$).

For **10a**: 1.16 (t, 6H, *J* 7.7 Hz, CH_3), 3.26 (q, 4H, *J* 7.7 Hz, CH_2), 6.15 (s, 1H, H^3), 7.65–7.95 (m, 2H, $H^{9,10}$), 7.95–8.40 (m, 4H, $H^{5,6,8,11}$), 12.60 (br. s, 1H, NH).

For **11a**: 1.12 (t, 6H, *J* 7.7 Hz, CH_3–C–N), 1.50 (t, 3H, *J* 7.7 Hz, CH_3–CO), 3.30 (q, 4H, *J* 7.7 Hz, CH_2N), 4.73 (q, 2H, *J* 7.7 Hz, CH_2O), 6.50 (s, 1H, H^3), 7.65–7.90 (m, 2H, $H^{9,10}$), 8.10–8.40 (m, 4H, $H^{5,6,8,11}$).



Scheme 2

by heating **9b** for 5–180 min at 80–100 °C with piperidine, $BuSH/Na_2CO_3$ in dioxane and $NaCH(COOEt)_2$, respectively.

In conclusion, the addition of $HNRR^1$ to ethyl (1-amino-9,10-anthraquinon-2-yl)propiolate **2** and subsequent cyclization of the adducts **3** to form a 2-chloro-4-dialkyl(or alkyl)amino-substituted pyridine ring, followed by nucleophilic substitution of the chlorine atom in this heterocycle, offer a novel route to the synthesis of 2-functionalized 4-dialkyl(or alkyl)aminonaphtho-[2,3-*h*]quinoline-7,12-diones **1**.

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