

Synthesis of 3-Alkenyl-1-azaanthraquinones *via* Diels-Alder and Electron Transfer Reactions

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Abstract: A convenient route to 3-alkenyl-1-azaanthraquinones *via* a hetero Diels-Alder reaction between an azadiene and naphthoquinone, a free radical chlorination and an electron transfer reaction is reported.

Keywords: Naphthoquinone, azadiene, azaanthraquinone, Diels-Alder, S_{RN}1.

Introduction

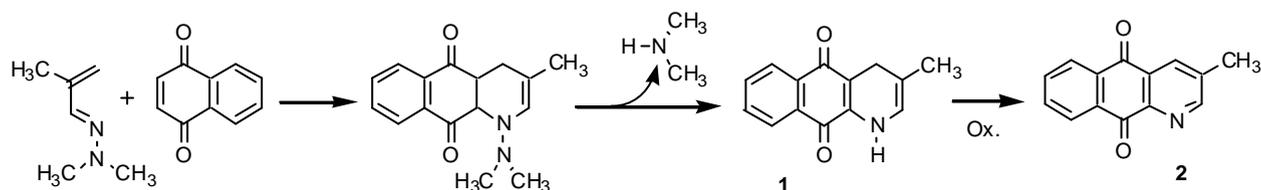
The anthracyclines (doxorubicin, daunorubicin) play an important role in the treatment of many human lymphomas, leukemia and solid tumors [1, 2]. However, their clinical use is limited mainly by two major problems, namely their cumulative cardiotoxicity and the appearance of intrinsic and acquired drug resistance. The search for new analogues having better therapeutic efficacy led us to synthesize 3-alkenyl-1-azaanthraquinone derivatives.

Results and Discussion

The first step proceeds *via* a hetero Diels-Alder reaction between an azadiene and naphthoquinone. Various groups have studied such a reaction, including its regioselectivity when it was performed using

unsymmetrical quinones [3]. In this case the [4 + 2] cycloaddition between 1-dimethylamino-3-methyl-1-aza-1,3-butadiene and naphthoquinone was followed by elimination of dimethylamine and oxidation to afford the aromatized 3-methyl-1-azaanthraquinone (**2**) (Scheme 1).

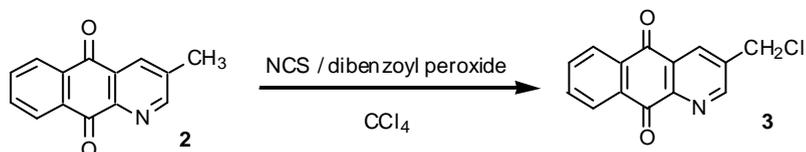
Scheme 1.



By performing the reaction in acetonitrile at room temperature for 24 hours and using 2 equivalents of naphthoquinone, Serckx-Poncin [4] obtained, in an one pot synthesis, the aromatized adduct **2** in 92% yield. Lee [5] modified this process by replacing the excess naphthoquinone with stirring in the presence of silica gel to effect the oxidation. Compound **2** was then obtained in 51% yield. Using the Serckx-Poncin procedure with a slight excess (1.2 eq.) of naphthoquinone we only obtained compound **1** in 55% yield, resulting from the cycloaddition followed by the elimination of dimethylamine, instead of the 3-methyl-1-azaanthraquinone (**2**). Oxidation was performed by stirring in refluxing ethanol as described for the reaction with 5-hydroxynaphthoquinone [6]. Derivative **2** was isolated in 95% yield after purification by chromatography. In order to optimize this reaction we have treated directly the crude residue, after acetonitrile removal, with boiling ethanol. A simple recrystallization from ethanol led to **2** in 90% yield. The advantage of such a procedure lies in the fact that you don't have to use a 2 eq. excess of naphthoquinone, in one hand and you can obtain **2** without any purification by column chromatography, on the other hand.

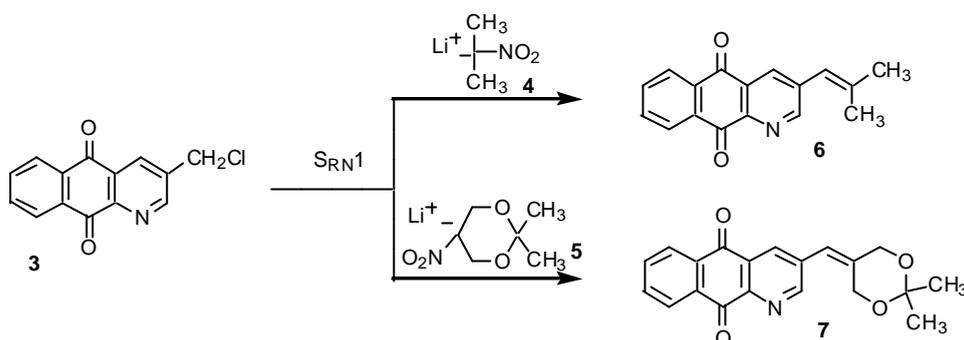
The 3-methyl group was then halogenated according to the Newkome procedure [7]. (Scheme 2). Various experimental conditions, using *N*-chlorosuccinimide as reactant, were tried in an attempt to increase the yield of the reaction. The best yield of **3** was 31% along with the starting material **2** (47%) and trace amounts of the dihalogenated derivative were also isolated.

Scheme 2.



3-Chloromethyl-1-azaanthraquinone (**3**) was then reacted with the lithium salts of 2-nitropropane or 2,2-dimethyl-5-nitro-1,3-dioxane *via* an $S_{RN}1$ mechanism. Using Kornblum's conditions [8,9] in degassed DMF, only the ethylenic derivative, resulting from by a base promoted nitrous acid elimination of the corresponding *C*-alkylated product, was isolated in good yield (Scheme 3).

Scheme 3.



Conclusions

A first key-step has been optimized, providing 3-methyl-1-azaanthraquinone (2) in high yield after an easier work-up than those previously described in the literature. Thus, this work has shown that such a pathway is a convenient route for the synthesis of 3-alkenyl-1-azaanthraquinones and it is currently being extended to various anions to produce a new series of azaanthraquinones which will be assessed for biological activity towards various tumor cell lines.

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Experimental

General

Melting points were determined on a Büchi B540 apparatus and are uncorrected. Elemental analyses were performed by the Centre de Microanalyses of the University of Aix-Marseille 3. Both ^1H - and ^{13}C -NMR spectra were determined on a Bruker ARX 200 spectrometer. The ^1H - chemical shifts were reported as parts per million downfield from tetramethylsilane (Me_4Si) and the ^{13}C - chemical shifts were referenced to the CDCl_3 solvent peak (76.9 ppm). Silica gel 60 (Merck, 230-400 mesh) was used for column chromatography. Thin-layer chromatography was performed with silica gel Merck 60F-254 (0.25 mm layer thickness).

Synthesis of 3-methyl-1-azaanthraquinone (2).

Naphthoquinone (1 g, 32.2 mmol) was added to a solution of 1-dimethylamino-3-methyl-1-aza-1,3-butadiene (3 g, 26.8 mmol) in acetonitrile (120 mL). The reaction mixture, which rapidly turned dark red, was

stirred for 20 h at room temperature. Then, acetonitrile was removed under reduced pressure, the crude residue was dissolved in ethanol (110 mL) and the reaction mixture was stirred for 20 h in refluxing ethanol. After cooling at room temperature, it was evaporated and recrystallized from ethanol, to afford 5.38 g (90% yield) of **2** as yellow needles, m.p. 244 °C; $^1\text{H-NMR}$ (CDCl_3) δ 2.50 (s, 3H, CH_3), 7.68-7.81 (m, 2H, $\text{H}_{6,7}$), 8.13-8.24 (m, 1H, H_5 or δ), 8.26-8.39 (m, 2H, H_4 , H_5 or δ), 8.85 (d, 1H, $J = 2.0$ Hz, H_2). $^{13}\text{C NMR}$ (CDCl_3) δ 18.92 (CH_3), 127.21 (CH), 127.88 (CH), 130.16 (C), 132.81 (C), 133.50 (C), 134.39 (CH), 134.67 (CH), 135.05 (CH), 138.92 (C), 146.84 (C), 155.83 (CH), 181.57 (C), 183.04 (C).

Free radical chlorination of 2: preparation of 3-chloromethyl-1-azaanthraquinone (3).

2 (3 g, 13.4 mmol), *N*-chlorosuccinimide (3.63 g, 27.18 mmol) and a catalytic amount of dibenzoyl peroxide were stirred in refluxing carbon tetrachloride (200 mL) for 2 h in the presence of two 60 W tungsten lamps. After cooling to room temperature, the solvent was removed under reduced pressure. The crude residue was purified by chromatography on a silica gel column, eluting with ethyl acetate, to yield 1.07 g (31%) of 3-chloromethyl-1-azaanthraquinone (**3**) as brown crystals, m.p. 160 °C; Rf: 0.75 (ethyl acetate). IR (KBr) cm^{-1} : 1680, 1585. $^1\text{H-NMR}$ (CDCl_3) δ 4.75 (s, 2H, CH_2Cl), 7.80-7.88 (m, 2H, $\text{H}_{6,7}$), 8.26-8.33 (m, 1H, H_5 or δ), 8.34-8.42 (m, 1H, H_5 or δ), 8.64 (d, 1H, $J = 2.1$ Hz, H_4), 9.09 (d, 1H, $J = 2.1$ Hz, H_2); $^{13}\text{C-NMR}$ (CDCl_3) δ 42.35 (CH_2), 126.86 (CH), 127.22 (CH), 130.42 (C), 132.79 (C), 133.66 (C), 134.72 (CH), 134.79 (CH), 135.02 (CH), 138.41 (C), 148.35 (C), 154.71 (CH), 180.89 (C), 182.57 (C); Anal. Calcd for $\text{C}_{14}\text{H}_8\text{ClNO}_2$ (257.67): C, 65.26; H, 3.13; N, 5.44%. Found: C, 65.19; H, 3.22; N, 5.37%.

Preparation of nitronate lithium salts 4 and 5.

The synthesis of the lithium salts of 2-nitropropane and 2,2-dimethyl-5-nitro-1,3-dioxane (**4** and **5**) has been previously described [10].

$S_{RN}1$ reactions of chloride 3 with the lithium salts 4 and 5: preparation of 3-(2-methylpropenyl)-benzo[g]quinoline-5,10-dione (6) and 3-(2,2-dimethyl-[1,3]dioxan-5-ylidenemethyl)-benzo[g]quinoline-5,10-dione (7).

To a solution of 2-nitropropane lithium salt (**4**) (370 mg, 3.88 mmol) or 2,2-dimethyl-5-nitro-1,3-dioxane lithium salt (**5**) in dry DMF (10 mL), the chloride **3** (250 mg, 0.97 mmol) was added under nitrogen and anhydrous conditions. The reaction mixture was irradiated with two 60 W tungsten lamps and stirred at room temperature for 20 h. Then, it was poured into water (100 mL). The aqueous solution was extracted with dichloromethane (3 x 50 mL). The organic extracts were washed with water (6 x 300 mL), dried over anhydrous Na_2SO_4 and evaporated under vacuum. For the reaction with **4**, the crude residue was purified by chromatography on a silica gel column eluting with ethyl acetate. After recrystallization from isopropanol, 190

mg (75% yield) of the ethylenic derivative 3-(2-methyl-propenyl)-benzo[g]quinoline-5,10-dione (**6**) was obtained as a brown solid, m.p. 137 °C; Rf: 0.77 (ethyl acetate). IR (KBr) cm^{-1} : 2900, 1680, 1570. $^1\text{H-NMR}$ (CDCl_3) δ 1.97 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 6.35 (broad s, 1H, ethylenic H), 7.75-7.88 (m, 2H, $\text{H}_{6,7}$), 8.23-8.31 (m, 1H, H_5 or δ), 8.35-8.43 (m, 2H, H_4 , H_5 or δ), 8.91 (d, 1H, $J = 2.1$ Hz, H_2); $^{13}\text{C-NMR}$ (CDCl_3) δ 19.83 (CH_3), 27.34 (CH_3), 120.53 (CH), 127.09 (CH), 127.73 (CH), 130.02 (C), 132.76 (C), 133.48 (C), 133.54 (CH), 134.24 (CH), 134.57 (CH), 138.75 (C), 143.15 (C), 145.90 (C), 155.07 (CH), 181.28 (C), 182.94 (C); Anal. Calcd for $\text{C}_{17}\text{H}_{13}\text{NO}_2$ (263.29): C, 77.55; H, 4.98; N, 5.32%. Found: C, 77.59; H, 4.96; N, 5.18%.

For the reaction with **5**, the crude residue was directly recrystallized from isopropanol yielding 230 mg (71%) of 3-(2,2-dimethyl-[1,3]dioxan-5-ylidenemethyl)-benzo[g]quinoline-5,10-dione (**7**) as a brown solid, m.p. 169 °C; IR (KBr) cm^{-1} : 2980, 1680, 1575. $^1\text{H-NMR}$ (CDCl_3) δ 1.45 (s, 6H, 2 CH_3), 4.46 (broad s, 2H, CH_2O), 4.69 (broad s, 2H, CH_2O), 6.39 (broad s, 1H, ethylenic H), 7.80-7.88 (m, 2H, $\text{H}_{6,7}$), 8.25-8.32 (m, 2H, H_4 , H_5 or δ), 8.35-8.43 (m, 1H, H_5 or δ), 8.85 (d, 1H, $J = 2.1$ Hz, H_2); $^{13}\text{C-NMR}$ (CDCl_3) δ 23.78 (2 CH_3), 60.53 (CH_2), 64.06 (CH_2), 99.87 (C), 117.55 (CH), 127.24 (CH), 127.88 (CH), 130.08 (C), 132.70 (C), 133.47 (C), 133.68 (CH), 134.47 (CH), 134.81 (CH), 136.08 (C), 144.36 (C), 146.64 (C), 154.60 (CH), 181.09 (C), 182.62 (C); Anal. Calcd for $\text{C}_{20}\text{H}_{17}\text{NO}_4$ (335.35): C, 71.63; H, 5.11; N, 4.18%. Found: C, 71.50; H, 5.18; N, 4.09%.

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Samples Availability: Available from the authors.