An Original One-Pot Synthesis of Dialkyl-Substituted Anthraquinones

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Abstract: 2,3-Bis(chloromethyl)-1,4-naphthoquinone reacts with primary nitroalkanes in a one-pot synthesis to give a series of anthraquinones bearing two *n*-alkyl substituents at C-2 and C-3 in good yields. The reaction is shown to proceed by two consecutive $S_{RN}1$ processes followed by base-promoted nitrous acid elimination, electrocyclic ring-closure and dehydrogenation. In comparison with the classical Diels-Alder reaction, the advantage of this route is the simplicity of starting-material preparation.

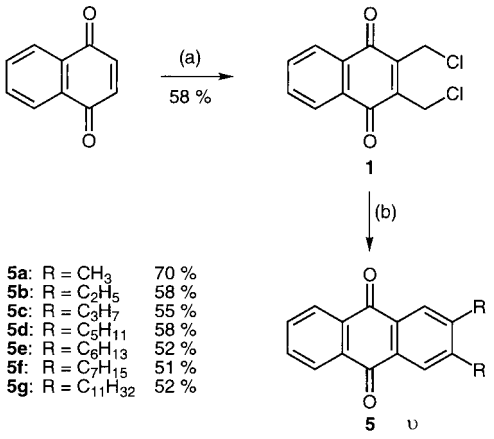
Due to the presence of the quinone ring in numerous biologically active compounds[1,2] as well as to their use as auxiliaries in organic synthesis and in dye industry,[3,4] quinonoid compounds continue to attract interest. Quinones, and particularly anthracyclines such as adriamycin and daunorubicin, are effective in the palliative management of a wide variety of human malignancies. However, intrinsic and acquired drug resistance as well as undesired effects such as cumulative dose-dependent cardiotoxicity[5] limit their clinical utilization. As bioreductible agents, they constitute potential substrates for the radical nucleophilic substitution ($S_{RN}1$ reaction).[6] In the anthraquinone series, the method of choice for the synthesis of dialkyl-substituted compounds[7,8] is the Diels-Alder reaction between 1,4-naphthoquinone and a 1,3-diene, followed by dehydrogenation of the obtained primary tricyclic adduct.[9] However, the limitation of this method was the difficult preparation of 2,3-dialkyl-1,3-butadienes, which are usually synthesized by alkylation of the dianion of 2,3-dimethyl-1,3-butadiene with 1-halo-alkanes.[7] Indeed, Bates has reported the formation of this dianion by deprotonation of 2,3-dimethyl-1,3-butadiene with a mixture of *n*-butyllithium and potassium *tert*-butoxide in pentane.[10] To optimize the yield of Diels-Alder reaction, the resulting dienes must be purified by distillation.[7]

In connection with our program directed toward the development of novel synthetic quinone congeners as anticancer agents, we report here a new and easy one-pot preparative method to produce dialkyl-substituted anthraquinones.

2,3-Bis(chloromethyl)-1,4-naphthoquinone (**1**) was prepared by saturating a cooled solution of 1,4-naphthoquinone and aqueous formaldehyde in glacial acetic acid with dry hydrogen chloride, for 2 h, according to Thomson's procedure.[11] Nitroalkanes were commercially available or easily obtained in excellent yields (70-80 %) from primary amines by oxidation with *m*-chloroperbenzoic acid in refluxing 1,2-dichloroethane.[12]

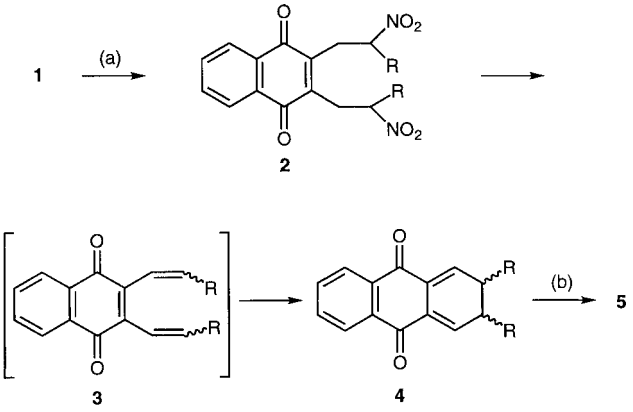
Treatment of the bis-chloride **1** (1 equiv) with the primary nitroalkanes (4 equiv) during 48 h, under standard $S_{RN}1$ reaction conditions (inert atmosphere, photostimulation) and in a phase-transfer system[13] (40 % tetrabutylammonium hydroxide in water and toluene), furnished 2,3-dialkylanthraquinones **5** in 52-70 % good yield.[14]

As reported previously,[15] two consecutive $S_{RN}1$ processes led to the bis-C-alkylation product **2**, which, in the presence of an anion excess, underwent double nitrous acid elimination to give the non-isolated bis-ethylenic product **3**. Electrocyclic ring-closure of the latter produced dihydroanthraquinone **4** that, after dehydrogenation,[16] gave the expected



Scheme 1. *Reagents* : (a) HCHO, HCl, AcOH, 2 h; (b) RCH_2NO_2 (4 equiv), NBu_4OH 40% in water, $C_6H_5CH_3$ degassed, hυ, 48 h

2,3-dialkylanthraquinone **5**. Use of nitroethane under the standard experimental conditions during 0.5 h with a 2:1 nitronate anion to bis-chloride ratio, allowed isolation of the bis-C-alkylation product **2a** in 32% yield along with 35 % of remaining starting material.[17] Treatment of **2a** in the presence of the appropriate nitronate anion (2 eq.) under the same experimental conditions during 24 h gave the required 2,3-dimethylanthraquinone (**5a**) in 65 % yield. A similar yield was observed in the presence of classical inhibitors[18] (*p*-dinitrobenzene, TEMPO or bubbling dioxygen) which indicates the absence of intramolecular SET reaction[19] for the transformation of **2a** into **5a**.



Scheme 2. *Reagents* : (a) RCH_2NO_2 (4 equiv.), NBu_4OH 40 % in water, $C_6H_5CH_3$ degassed, hv, 48 h; (b) dehydrogenation

In conclusion, compared to the published methods, this route is clearly the shortest and the most efficient known. It appears to be promising for the synthesis of dialkyl-substituted anthraquinones.

References and Notes

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(14) Typical procedure for the formation of **5**. Under nitrogen atmosphere, a solution of tetrabutylammonium hydroxide (1.6 M/ water, 5.00 mL, 7.8 mmol) was treated with a nitroalkane (7.8 mmol) for 1 h. A solution of 2,3-bis (chloromethyl)-1,4-naphthoquinone (**1**) (0.5 g, 1.95 mmol) in toluene (20 ml) was added and the mixture was irradiated with a 300 W sun lamp for 48 h at r.t. under an inert atmosphere. The organic layer was separated and the aqueous layer was extracted with toluene (3 x 10 ml). The combined organic layers were washed twice with water (20 ml), dried over $MgSO_4$ and removed under reduced pressure. Purification by chromatography on silica gel eluting with dichloromethane and recrystallization from ethanol gave 2,3-dialkylanthraquinone **5**. New products: **5b**, orange solid, mp 126 °C, ^{1}H NMR ($CDCl_3$) δ : 1.32 (t, *J* = 7.5, 6H, CH_3); 2.81 (q, *J* = 7.5, 4H, CH_2); 7.77 (m, 2H, 6-H, 7-H); 8.10 (s, 2H, 1-H, 4-H); 8.29 (m, 2H, 5-H, 8-H). ^{13}C NMR ($CDCl_3$) δ : 183.37 (CO); 149.15 (C-2, C-3); 133.84 (C-8a, C-10a); 133.69 (C-6, C-7); 131.51 (C-4a, C-9a); 127.06 (C-1, C-4); 126.98 (C-5, C-8); 25.80 (CH_2); 14.64 (CH_3). Anal. calcd for $C_{18}H_{16}O_2$ (264.32) : C, 81.79; H, 6.10. Found : C, 81.57; H, 6.05.
5g, orange solid, mp 66 °C, ^{1}H NMR ($CDCl_3$) δ : 0.88 (t, *J* = 6.0, 6H, CH_3); 1.28 (m, 32H, CH_2); 1.66 (m, 4H, CH_2CH_3); 2.76 (t, *J* = 7.6, 4H, benzylic CH_2); 7.76 (m, 2H, 6-H, 7-H); 8.07 (s, 2H, 1-H, 4-H); 8.30 (m, 2H, 5-H, 8-H). ^{13}C NMR ($CDCl_3$) δ : 183.37 (CO); 148.14 (C-2, C-3); 133.82 (C-8a, C-10a); 133.74 (C-6, C-7); 131.32 (C-4a, C-9a); 127.83 (C-1, C-4); 127.05 (C-5, C-8); 32.99, 31.90, 30.77, 29.70, 29.65, 29.62, 29.55, 29.47, 29.34, 22.67 (CH_2); 14.10 (CH_3). Anal. calcd for $C_{36}H_{52}O_2$ (516.81) : C, 83.67; H, 10.14. Found : C, 83.35; H, 10.34.

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(16) The compound **2a** is obtained by using typical procedure with nitroethane (0.293 g, 3.90 mmol). Orange solid, mp 106 °C (isopropanol), ^{1}H NMR ($CDCl_3$) δ : 1.69 (d, *J* = 6.6, 6H, CH_3); 3.13 (m, 4H, benzylic CH_2); 4.89 (m, 2H, CH); 7.75 (m, 2H, 6-H, 7-H); 8.08 (m, 2H, 5-H, 8-H). Anal. calcd for $C_{16}H_{16}N_2O_6$ (332.31) : C, 57.83; H, 4.85; N, 8.43. Found : C, 57.83; H, 4.80; N, 8.45.

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