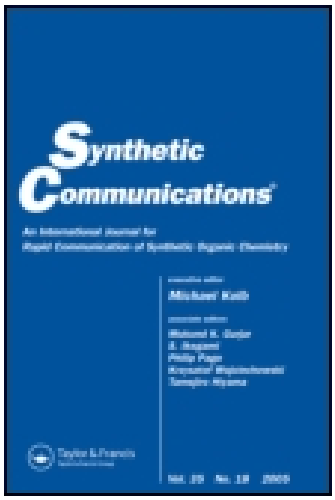

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

SYNTHESIS OF 2,3-DIALKYLQUINONES BY BIS-$S_{RN}1$ METHODOLOGY

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Published online: 09 Nov 2006.

To cite this article: Thierry Terme , José Maldonado , Michel P. Crozet & Patrice Vanelle (2001) SYNTHESIS OF 2,3-DIALKYLQUINONES BY BIS-$S_{RN}1$ METHODOLOGY, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 31:24, 3877-3883, DOI: 10.1081/SCC-100108240

To link to this article: http://dx.doi.org/10.1081/SCC-100108240

SYNTHETIC COMMUNICATIONS, 31(24), 3877–3883 (2001)

SYNTHESIS OF 2,3-DIALKYLQUINONES BY *BIS*-$S_{RN}1$ METHODOLOGY

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ABSTRACT

Three series of complex dialkylquinones were prepared by reacting *bis*(chloromethyl)quinones with simple and more complex nitronate anions under electron transfer reaction conditions.

Quinones represent a class of organic compounds possessing rich and fascinating chemistry. Many of them are important therapeutic agents,[1,2] quite often they serve as auxiliaries in organic synthesis and in the dye industry.[3,4] Mitomycin C is a representative of the group of bioreductive *bis*-alkylating antitumor agents and its reduction has been shown to result in the formation of reactive species which are able to alkylate DNA.[5,6] In the last few years, the interest in these compounds has been growing and new trial bioreductive anticancer agents that seem to be more powerful and with less undesired effects have been investigated.[7,8] In connection with our program directed toward the development of novel synthetic quinone congeners

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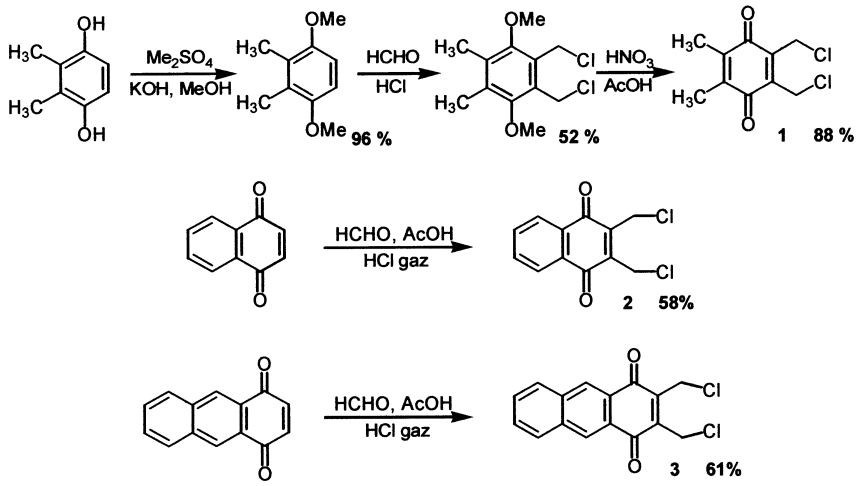
as anticancer agents,[9,10] we reported here the synthesis of three *bis*(chloromethyl)quinones and the study of their reactivity with simple and more complex nitronate anions leading to original and new dialkylquinones. 2,3-*Bis*(chloromethyl)-5,6-dimethyl-1,4-benzoquinone **1** was prepared in three steps from 2,3-dimethyl-1,4-hydroquinone. Whereas, the 2,3-*bis*(chloromethyl)-1,4-naphtho- **2** and 1,4-anthraquinone **3** were obtained from respectively 1,4-naphthoquinone and 1,4-anthraquinone according to Thomson's procedure,[11] by saturating a cooled solution of corresponding quinone and aqueous formaldehyde in glacial acetic acid with dry hydrogen chloride for 2 h (Scheme 1).

These *bis*(chloromethyl)quinones **1**–**3** reacted with 5 equivalents of 2-nitropropane anion **4a** under $S_{RN}1$ reaction conditions (inert atmosphere, photostimulation) and in a phase-transfer system (40% tetrabutylammonium hydroxide in water and dichloromethane) to give the corresponding *bis*-*C*-alkylated products **5a**–**7a** in good yields, after 10 min in benzoquinone series and after 20 min in naphtho- and anthraquinone series (Scheme 2). To confirm the nature of these mechanisms, the reactions of *bis*-chlorides **1**–**3** and **4a** were studied in presence of classical inhibitors. Addition of *p*-dinitrobenzene as radical anion scavenger, TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) as radical trap, $CuCl_2$ or bubbling dioxygen through the solution in the dark strongly decreased the yield of corresponding *bis*-*C*-alkylated product **5a**–**7a**. These experimental data indicated that these products were formed by a *bis*-$S_{RN}1$ mechanism.



Scheme 1.

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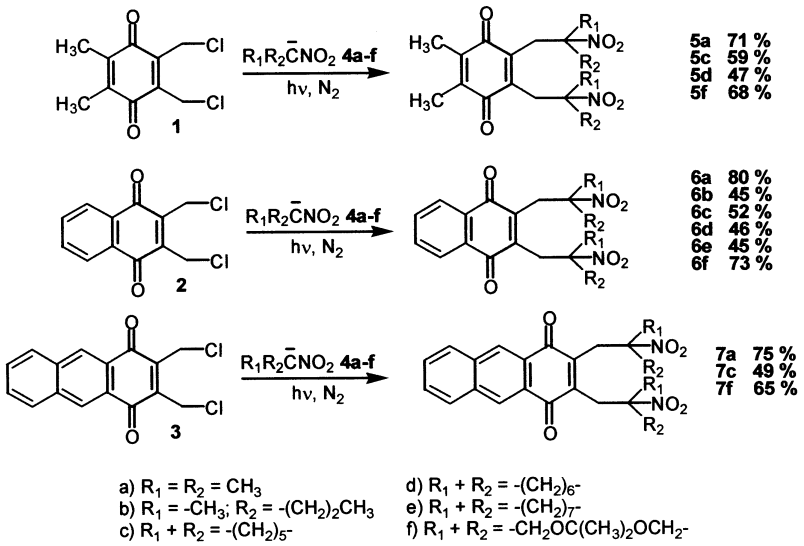

Scheme 2.

These *bis*-$S_{RN}1$ reactions were extended with various secondary nitronate anions **4b**–**f** (aliphatic, cyclic or heterocyclic) and allowed us to reach at three series of new highly branched dialkylquinones (Scheme 2).

The nitroalkanes were commercially available or prepared by oxidation of the corresponding amines with *m*-chloroperbenzoic acid in refluxing 1,2-dichloroethane by Gilbert and Borden procedure.[12] The nitroalkanes were purified by distillation or recrystallization. The 5-nitro-1,3-dioxane salt was prepared by the method[13] described previously from 2-hydroxymethyl-2-nitro-propane-1,3-diol, acetone and boron trifluoride diethyl etherate. Treatment with lithium methoxide split-off formaldehyde to give the corresponding salt. The extension reaction conditions were determined by the nitronate anion used. For aliphatic and cyclic nitronate anions **4b**–**e**, we have utilized, as for 2-nitropropane anion, the classical conditions: phase-transfer system with 40% of tetrabutylammonium hydroxide in water and dichloromethane, 5 equivalents of nitronate anion during 10 min in benzoquinone series and during 20 min for the other series. Whereas, with the 5-nitro-1,3-dioxane anion **4f**, the reactions were carried out in methanol.

In conclusion, we have extended the *bis*-$S_{RN}1$ reactions of three *bis*(chromethyl)quinones with various nitronate anions. Three series of highly branched dialkylquinones were synthesized in good yields. Study of the antitumor activity of related compounds is under active investigation.

EXPERIMENTAL

Melting points were determined on Büchi B-540 and are uncorrected. Elemental analyses were performed by the Centre de Microanalyses of the University of Aix-Marseille 3. Both ^{1}H and ^{13}C NMR spectra were determined on Bruker ARX 200 spectrometer. The ^{1}H chemical shifts were reported as parts per million downfield from tetramethylsilane (Me_4Si), and the ^{13}C chemical shifts were referenced to the solvents peaks: $CDCl_3$ (76.9 ppm) or Me_2SO-d_6 (39.6 ppm). The following adsorbent was used for column chromatography: silica gel 60 (Merck, 230–400 mesh). Thin-layer chromatography was performed with silica gel Merck 60F-254 (0.25 mm layer thickness).

General procedure for *bis*-$S_{RN}1$ reaction with aliphatic and cyclic nitronate anions. Under nitrogen atmosphere, a solution of tetrabutylammonium hydroxide (1.6 M/water, 6.4 mL, 9.75 mmol) was treated with nitroalkane (9.75 mmol) for 1 h. A solution of corresponding 2,3-*bis*(chloromethyl)-1,4-quinone **1**–**3** (1.95 mmol) in dichloromethane (20 mL) was added and the mixture was irradiated with a 300 W sun lamp for 20 min (naphtho- and anthraquinone series) or 10 min (benzoquinone series) at room temperature under an inert atmosphere. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×10 mL). The combined organic layers were washed twice with water (30 mL), dried over $MgSO_4$ and removed under reduced pressure. Purification by chromatography on silica gel eluting with dichloromethane and recrystallization from ethanol gave the corresponding dialkylquinone **5**–**7**.

General procedure for *bis*-$S_{RN}1$ reaction with heterocyclic nitronate anion. 2,2-Dimethyl-5-nitro-1,3-dioxane lithium salt (1.6 g, 9.75 mmol) was added to a solution of corresponding 2,3-*bis*(chloromethyl)-1,4-quinone **1**–**3** (1.95 mmol) in dry methanol (30 mL). The reaction was allowed to proceed for 20 min (benzo- and naphthoquinone series) or 24 h (anthraquinone series) at room temperature under nitrogen and in the presence of light (300 W sun lamp). After reaction, methanol was removed under reduced pressure and water (50 mL) was added to the residue which was extracted with dichloromethane (3×50 mL). The combined organic layers were washed with water (2×30 mL), dried over $MgSO_4$ and removed under reduced pressure. Purification by chromatography on silica gel eluting with dichloromethane and recrystallization from ethanol gave the corresponding 2,3-*bis*(2,2-dimethyl-5-nitro-1,3-dioxan-5-ylmethyl)-1,4-quinone **5f**–**7f**.

2,3-*Bis*(2-methyl-2-nitropropyl)-5,6-dimethyl-1,4-benzoquinone (5a). Yellow solid, mp 156°C (ethanol). ^{1}H NMR ($CDCl_3$): δ 1.54 (s, 12H), 2.03 (s, 6H), 3.14 (s, 4H). ^{13}C NMR ($CDCl_3$): δ 12.6, 26, 36, 87.8, 141.2, 142.1,

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186.4. Anal. Calcd for $C_{16}H_{22}N_2O_6$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.76; H, 6.56; N, 8.23.

2,3-*Bis*(2-nitrocyclohex-2-ylmethyl)-5,6-dimethyl-1,4-benzoquinone (5c). Yellow solid, mp 194°C (ethanol). ^{1}H NMR ($CDCl_3$): δ 1.21 (m, 4H), 1.55 (m, 12H), 2.02 (s, 6H), 2.33 (m, 4H), 2.96 (s, 4H). ^{13}C NMR ($CDCl_3$): δ 12.6, 22.2, 24.2, 34.8, 36.5, 91.8, 141.2, 142.1, 186.1. Anal. Calcd for $C_{22}H_{30}N_2O_6$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.11; H, 7.28; N, 6.74.

2,3-*Bis*(2-nitrocyclohept-2-ylmethyl)-5,6-dimethyl-1,4-benzoquinone (5d). Yellow solid, mp 111°C (ethanol). ^{1}H NMR ($CDCl_3$): δ 1.55 (m, 16H), 1.84 (m, 4H), 2.05 (s, 6H), 2.33 (m, 4H), 3.05 (s, 4H). ^{13}C NMR ($CDCl_3$): δ 12.6, 22.7, 29.4, 36.5, 37.1, 95.3, 141.2, 142.1, 186.4. Anal. Calcd for $C_{24}H_{34}N_2O_6$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.61; H, 7.66; N, 6.24.

2,3-*Bis*(2,2-dimethyl-5-nitro-1,3-dioxan-5-ylmethyl)-5,6-dimethyl-1,4-benzoquinone (5f). Brown solid, mp 225°C (ethanol). ^{1}H NMR ($CDCl_3$): δ 1.36 (s, 6H), 1.50 (s, 6H), 2.02 (s, 6H), 3.10 (s, 4H), 4.01 (d, J = 12.9 Hz, 4H), 4.27 (d, J = 12.9 Hz, 4H). ^{13}C NMR ($CDCl_3$): δ 12.6, 22, 24.4, 29.5, 63.9, 84.3, 99, 141.4, 143.1, 186.9. Anal. Calcd for $C_{22}H_{30}N_2O_{10}$: C, 54.77; H, 6.27; N, 5.81. Found: C, 54.75; H, 6.32; N, 5.77.

2,3-*Bis*(2-methyl-2-nitropropyl)-1,4-naphthoquinone (6a). Yellow solid, mp 151°C (ethanol). ^{1}H NMR ($CDCl_3$): δ 1.51 (s, 12H), 3.24 (s, 4H), 7.68 (m, 2H), 8.01 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 26.5, 36.6, 87.9, 126.8, 131.5, 134.2, 144.9, 184.1. Anal. Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 59.98; H, 5.51; N, 7.68.

2,3-*Bis*(2-methyl-2-nitropentyl)-1,4-naphthoquinone (6b). Yellow solid, mp 116°C (ethanol). ^{1}H NMR ($CDCl_3$): δ 0.93 (t, J = 7 Hz, 6H), 1.16–1.45 (m, 4H), 1.46 (s, 6H), 1.77 (m, 2H), 2.08 (m, 2H), 3.22 (d, J = 14.3 Hz, 2H), 3.34 (d, J = 14.3 Hz, 2H), 7.74 (m, 2H), 8.08 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 13.9, 17.4, 21.8, 36, 42.3, 91.3, 126.8, 131.6, 134.1, 145, 184.2. Anal. Calcd for $C_{22}H_{28}N_2O_6$: C, 63.45; H, 6.78; N, 6.73. Found: C, 63.40; H, 6.79; N, 6.66.

2,3-*Bis*(2-nitrocyclohex-2-ylmethyl)-1,4-naphthoquinone (6c). Yellow solid, mp 192°C (ethanol). ^{1}H NMR ($CDCl_3$): δ 1.20 (m, 4H), 1.63 (m, 12H), 2.38 (m, 4H), 3.13 (s, 4H), 7.74 (m, 2H), 8.08 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 22.2, 24.2, 34.8, 36.7, 91.7, 126.8, 131.5, 134, 144.7, 183.8. Anal. Calcd for $C_{24}H_{28}N_2O_6$: C, 65.44; H, 6.41; N, 6.36. Found: C, 65.45; H, 6.35; N, 6.33.

2,3-*Bis*(2-nitrocyclohept-2-ylmethyl)-1,4-naphthoquinone (6d). Yellow solid, mp 132°C (ethanol). ^{1}H NMR ($CDCl_3$): δ 1.55 (m, 16H), 1.89 (m, 4H), 2.36 (m, 4H), 3.21 (s, 4H), 7.75 (m, 2H), 8.07 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 22.7, 29.4, 36.7, 37.1, 95.5, 126.8, 131.6, 134, 144.9, 184.1. Anal. Calcd for $C_{26}H_{32}N_2O_6$: C, 66.65; H, 6.88; N, 5.98. Found: C, 66.60; H, 6.89; N, 5.94.

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2,3-*Bis*(2-nitrocyclooct-2-ylmethyl)-1,4-naphthoquinone (6e). Orange solid, mp 148°C (ethanol). ^{1}H NMR ($CDCl_3$): δ 1.55 (m, 20H), 1.97 (m, 4H), 2.24 (m, 4H), 3.17 (s, 4H), 7.73 (m, 2H), 8.07 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 22.8, 24.8, 27.6, 32.2, 35.4, 95.8, 126.8, 131.6, 134, 145.3, 184. Anal. Calcd for $C_{28}H_{36}N_2O_6$: C, 67.72; H, 7.31; N, 5.64. Found: C, 67.74; H, 7.28; N, 5.60.

2,3-*Bis*(2,2-dimethyl-5-nitro-1,3-dioxan-5-ylmethyl)-1,4-naphthoquinone (6f). Brown solid, mp 234°C (ethanol). ^{1}H NMR ($CDCl_3$): δ 1.37 (s, 6H), 1.52 (s, 6H), 3.29 (s, 4H), 4.08 (d, J = 12.8 Hz, 4H), 4.32 (d, J = 12.8 Hz, 4H), 7.76 (m, 2H), 8.08 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 22, 24.4, 29.6, 64, 84.4, 99, 126.9, 131.3, 134.4, 143.8, 183.8. Anal. Calcd for $C_{24}H_{28}N_2O_{10}$: C, 57.14; H, 5.59; N, 5.55. Found: C, 57.08; H, 5.62; N, 5.60.

2,3-*Bis*(2-methyl-2-nitropropyl)-1,4-anthraquinone) (7a). Orange solid, mp 191°C (ethanol). ^{1}H NMR ($CDCl_3$): δ 1.62 (s, 12H), 3.38 (s, 4H), 7.70 (m, 2H), 8.04 (m, 2H), 8.64 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 26.5, 36.5, 88, 127.8, 129.4, 129.7, 130.2, 135, 146.4, 183.7. Anal. Calcd for $C_{22}H_{22}N_2O_6$: C, 64.38, H, 5.40; N, 6.83. Found: C, 64.36; H, 5.35; N, 6.74.

2,3-*Bis*(2-nitrocyclohexan-2-ylmethyl)-1,4-anthraquinone (7c). Orange solid, mp 197°C (ethanol). ^{1}H NMR ($CDCl_3$): δ 1.20 (m, 4H), 1.66 (m, 12H), 2.39 (m, 4H), 3.33 (s, 4H), 7.76 (m, 2H), 8.09 (m, 2H), 8.68 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 22.2, 24.2, 34.8, 36.6, 91.8, 127.9, 129.4, 129.6, 130.1, 135, 146.2, 183.5. Anal. Calcd for $C_{28}H_{30}N_2O_6$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.49; H, 6.15; N, 5.75.

2,3-*Bis*(2,2-dimethyl-5-nitro-1,3-dioxan-5-ylmethyl)-1,4-anthraquinone (7f). Orange solid, mp 237°C (ethanol). ^{1}H NMR ($CDCl_3$): δ 1.38 (s, 6H), 1.56 (s, 6H), 3.41 (s, 4H), 4.15 (d, J = 12.8 Hz, 4H), 4.37 (d, J = 12.8 Hz, 4H), 7.78 (m, 2H), 8.09 (m, 2H), 8.69 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 22, 24.4, 29.7, 64.1, 84.5, 99, 127.8, 129.6, 129.8, 130, 135.3, 145.8, 183.5. Anal. Calcd for $C_{28}H_{30}N_2O_{10}$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.51; H, 5.42; N, 5.15.

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Received in the Netherlands February 12, 2001

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