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Unexpected reactivity in naphthoquinone series

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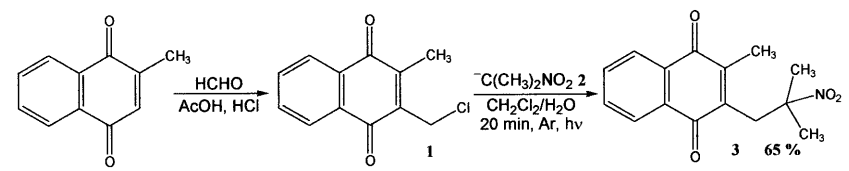
Abstract—An unexpected reactivity of 2-chloromethyl-3-methyl-1,4-naphthoquinone **1** with primary nitroalkanes in classical $S_{RN}1$ reaction conditions gives two series of new quinones: dialkyl anthraquinones and *C*-alkylated naphthoquinones.

The discovery of new drugs for the treatment and chemosuppression of malaria has become a priority in view of the continuing emergence and spread of multi-resistant strains of *Plasmodium falciparum*. Atovaquone is a novel hydroxynaphthoquinone which is the result of intensive synthetic efforts aimed at producing a metabolically stable compound with optimum activity against *Plasmodium falciparum* in vitro. Although first identified for its antimalarial activity, atovaquone was subsequently found to possess broad spectrum antiprotozoal activity and is now licensed for the treatment of opportunistic infections in patient with acquired immunodeficiency syndrome.[1] We have recently shown that 2-chloromethyl-3-methyl-1,4-naphthoquinone **1** (easily prepared from menadione according to Thomson's procedure[2]) reacts with 2-nitropropane anion **2** to give the *C*-alkylation product **3**.[3]

As a part of our program directed toward the study of electron transfer reactions to synthesize new biologically active naphthoquinones, we investigated the reactivity of **1** with nitroethane anion **4** and we obtained the required *C*-alkylation product **5a** and the unexpected anthraquinone **6a** (Table 1).



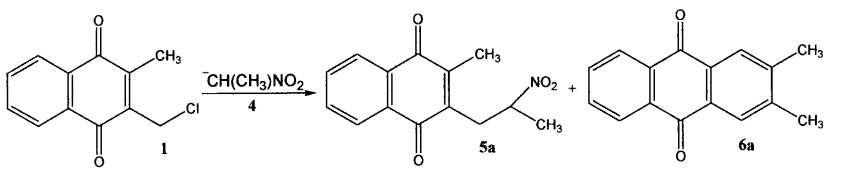


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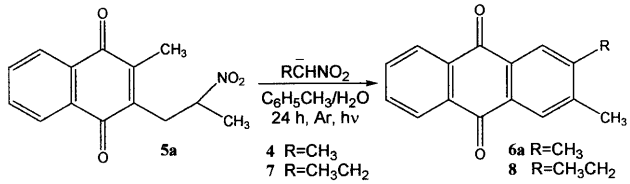
Table 1. Influence of experimental conditions in the reaction of **1** and **4**[a]

Entry	Mol. equiv. of **4**	Conditions[b]	Yield %	
			5a	**6a**
1	1.0 equiv.	CH_2Cl_2/H_2O, 20 min	45	0
2	2.0 equiv.	CH_2Cl_2/H_2O, 20 min	34	0
3	3.0 equiv.	CH_2Cl_2/H_2O, 20 min	22	16
4	4.0 equiv.	CH_2Cl_2/H_2O, 20 min	16	19
5	1.0 equiv.	$C_6H_5CH_3/H_2O$, 20 min	59	0
6	**1.0 equiv.**	**$C_6H_5CH_3/H_2O$, 10 min**	**85**	**0**
7	2.0 equiv.	$C_6H_5CH_3/H_2O$, 20 min	45	7
8	3.0 equiv.	$C_6H_5CH_3/H_2O$, 20 min	55	7
9	4.0 equiv.	$C_6H_5CH_3/H_2O$, 20 min	45	9
10	**4.0 equiv.**	**$C_6H_5CH_3/H_2O$, 48 h**	**0**	**39**

[a] All the reactions are performed at room temperature under argon and irradiated by fluorescent lamps (2×60 W).
[b] Phase-transfer conditions with NBu_4OH 40% in water.

The reaction of **1** with nitroethane anion **4**, in the conditions of entry 6, in presence of classical inhibitors (*p*-dinitrobenzene as radical-anion scavenger, 2,2,6,6-tetramethyl-1-piperidinyloxy or TEMPO as radical trap) gave effective inhibition, indicating a classical $S_{RN}1$ mechanism for the formation of **5a**.

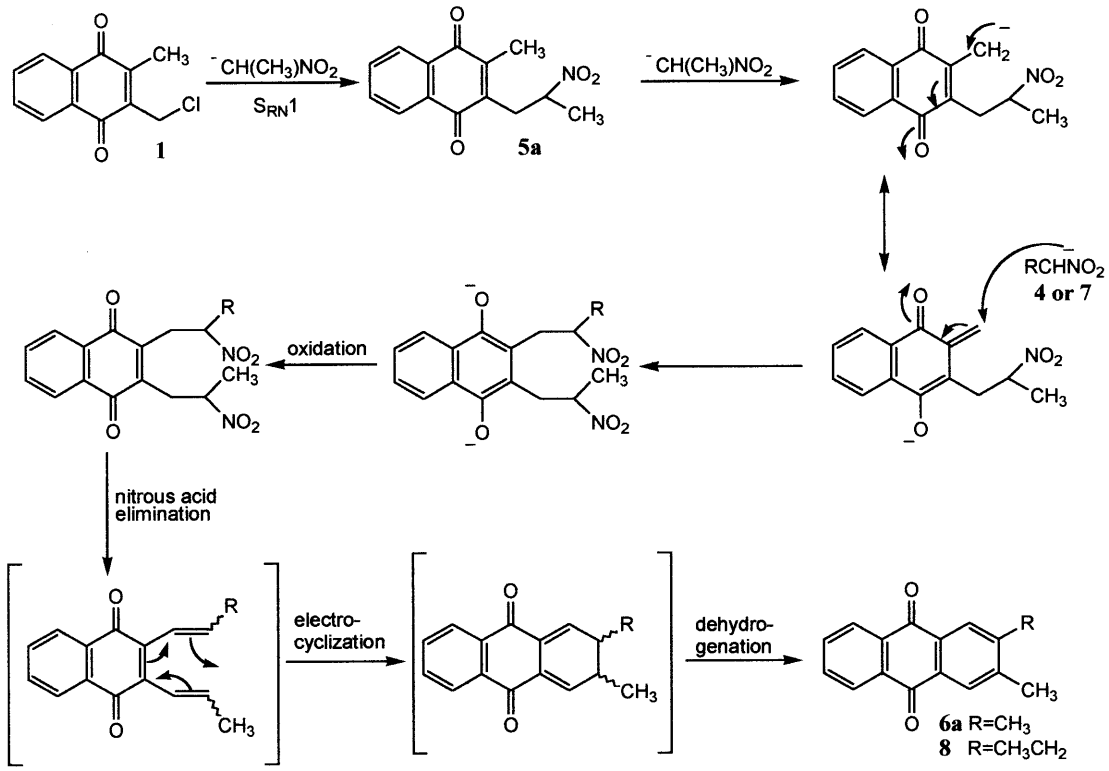
For explaining the formation of the unexpected anthraquinone **6a**, we studied the reactivity of **5a** with an excess (3.0 equiv.) of primary nitronate anion in phase-transfer conditions with toluene as solvent during 24 h. We obtained the 2,3-dimethylanthraquinone **6a** from nitroethane anion ($R = CH_3$) and the 2-ethyl-3-methyl-9,10-anthraquinone **8** from 1-nitropropane anion **7** ($R = CH_3CH_2$).[4]

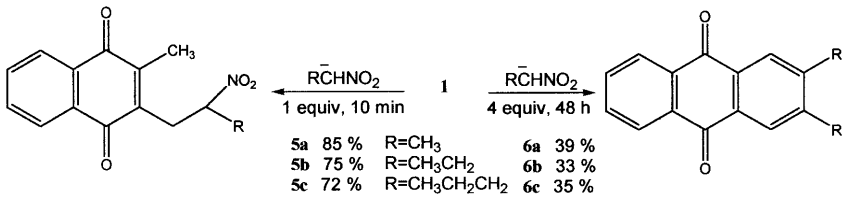


Moreover, for these reactions, a similar yield was observed in the presence of classical inhibitors (*p*-dinitrobenzene, TEMPO) indicating the absence of SET reaction for the transformation of **5a** into **6a** or **8**. All these experimental data led us to propose an original ionic mechanism for the formation of **6a** or **8** from **5a**. This mechanism was based on the participation of an anionic intermediate able to easily give a Michael acceptor which in the presence of an anion excess gives the bis-*C*-alkylated anion. As reported previously for annulation reactions in naphtho[5] and anthraquinone series,[6] after oxidation, nitrous acid elimination, electrocyclization and dehydrogenation, the corresponding anthraquinone (**6a** or **8**) was obtained.

After these original results, we generalized these reactions to various primary nitroalkanes and we prepared new series of *C*-alkylated products **5a**–**c**[7] and dialkylanthraquinones **6a**–**c**.[8]

In conclusion, we showed an unexpected reactivity of a 2-methylnaphthoquinone derivative and we proposed an original mechanism to explain this reactivity. Moreover, a series of new *C*-alkylated naphthoquinones was prepared from primary nitroalkanes according to a classical $S_{RN}1$ mechanism.





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2. Thomson, R. H. *J. Chem. Soc.* **1953**, 1196–1199.
3. Vanelle, P.; Terme, T.; Giraud, L.; Crozet, M. P. *Recent Res. Devel. Org. Chem.* **2000**, *4*, 1–28.
4. New product **8**: orange solid, mp 144°C (ethanol), ^{1}H NMR ($CDCl_3$) δ 1.28 (t, $J=7.6$ Hz, 3H); 2.44 (s, 3H); 2.74 (q, $J=7.6$ Hz, 2H); 7.75 (m, 2H); 8.01 (s, 1H); 8.04 (s, 1H); 8.26 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 14.6 (CH_3); 20.1 (CH_3); 25.8 (CH_2); 126.8 (CH); 126.9 (CH); 127 (CH); 127.1 (CH); 131.4 (C); 131.5 (C); 133.6 (CH); 133.7 (CH); 133.8 (C); 133.9 (C); 149.1 (C); 149.2 (C); 183.3 (C=O); 183.4 (C=O). Anal. calcd for $C_{17}H_{14}O_2$ (250.29): C, 81.58; H, 5.64. Found: C, 81.53; H, 5.61.
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6. Terme, T.; Crozet, M. P.; Giraud, L.; Vanelle, P. *Tetrahedron* **2000**, *56*, 1097–1101.
7. Typical procedure for **5a**–**c**. Under argon atmosphere, a solution of tetrabutylammonium hydroxide (40% in water, 2.6 ml, 4 mmol) was treated with a nitroalkane (4 mmol) for 1 h. A solution of 2-chloromethyl-3-methyl-1,4-naphthoquinone **1** (0.88 g, 4 mmol) in toluene (30 ml) was added and the mixture was irradiated with 300 W sun lamp for 10 min under an inert atmosphere. The organic layers were washed twice with water, dried over $MgSO_4$ and removed under reduced pressure. Purification by chromatography on silica gel eluting with dichloromethane and recrystallization from isopropyl alcohol gave *C*-alkylated product **5**. New derivatives: **5a**, Yellow solid, mp 84°C, ^{1}H NMR ($CDCl_3$) δ 1.6 (d, $J=6.7$ Hz, 3H); 2.15 (s, 3H); 3.1–3.3 (m, 2H); 4.97 (m, 1H); 7.78 (m, 2H); 8.01 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 12.9 (CH_3); 19.3 (CH_3); 33.1 (CH_2); 81.8 (CH); 126.2 (CH); 126.4 (CH); 131.5 (C); 131.8 (C); 133.6 (CH); 133.7 (CH); 140.5 (C); 146.4 (C); 183.4 (C=O); 183.5 (C=O). Anal. calcd for $C_{14}H_{13}NO_4$ (259.26): C, 64.86; H, 5.05; N, 5.40. Found: C, 64.78; H, 5.07; N, 5.29. **5b**, orange solid, mp 61°C, ^{1}H NMR ($CDCl_3$) δ 0.96 (t, $J=7.3$ Hz, 3H); 1.88–2.08 (m, 2H); 2.11 (s, 3H); 3.10–3.22 (m, 2H); 4.79 (m, 1H); 7.64 (m, 2H); 7.98 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3); 16.4 (CH_3); 19.4 (CH_2); 21.1 (CH_2); 81.7 (CH); 126.6 (CH); 126.9 (CH); 131.5 (C); 131.6 (C); 134.2 (CH); 134.4 (CH); 142.1 (C); 144.3 (C); 181.6 (C=O); 184.5 (C=O). Anal. calcd for $C_{15}H_{15}NO_4$ (273.28): C, 65.92; H, 5.53; N, 5.13. Found: C, 65.91; H, 5.63; N, 5.17. **5c**, orange solid, mp 51°C, ^{1}H NMR ($CDCl_3$) δ 0.97 (t, $J=7.3$ Hz, 3H); 1.32–1.5 (m, 2H); 1.75–1.90 (m, 2H); 2.17 (s, 3H); 3.10–3.22 (m, 2H); 4.81 (m, 1H); 7.63 (m, 2H); 8.07 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 13.1 (CH_3); 16.3 (CH_3); 19.9 (CH_2); 23.2 (CH_2); 24.1 (CH_2); 81.7 (CH); 126.6 (CH); 126.9 (CH); 131.5 (C); 131.6 (C); 134.2 (CH); 134.4 (CH); 142.1 (C); 144.3 (C); 181.6 (C=O); 184.5 (C=O). Anal. calcd for $C_{16}H_{17}NO_4$ (287.31): C, 66.89; H, 5.96; N, 4.88. Found: C, 66.85; H, 5.95; N, 4.82.
8. Typical procedure for **6a**–**c**. The procedure was similar to that for the formation of **5a**–**c**, except that the reaction time was 48 h and 4 equivalents of nitronate anion were used. The same purification gave the 2,3-dialkylanthraquinone **6a**–**c**.