Pergamon

Tetrahedron Letters, Vol. 37, No. 19, pp. 3323-3324, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00541-2

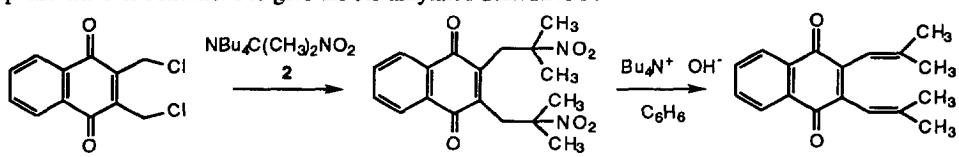
First Bis-$S_{RN}1$ in Naphthoquinone Series

Patrice Vanelle[a]*, Santa Donini[a], Thierry Terme[a], José Maldonado[a]
Christine Roubaud[b] and Michel P. Crozet[b]*

[a]Laboratoire de Chimie Organique, Faculté de Pharmacie, 27 Bd J. Moulin, 13385 Marseille Cedex 05, France
[b]Laboratoire de Chimie Moléculaire Organique, associé au CNRS, Faculté des Sciences et Techniques de Saint-Jérôme, B 562, Université de Droit, d'Economie et des Sciences d'Aix-Marseille, 13397 Marseille Cedex 20, France

Abstract: *The reaction of 2,3-bis(chloromethyl)-1,4-naphthoquinone with 2-nitropropane anion is shown to proceed by two consecutive $S_{RN}1$ reactions leading to the bis-C-alkylation product.*

$S_{RN}1$,[1] described in 1966 for *C*-alkylation of ambident nitronates by *p*-nitrobenzyl chloride has been extended to anthraquinone[2] and benzoquinone[3] alkylating agents. Mytomycin C is a representative of the group of bioreductive bis-alkylating antitumour agents and its reduction has been shown to result in the formation of reactive species, which are able to form DNA cross-links.[4] Much attention has recently been given to the development of other bis-alkylating agents and although 2,3-bis(chloromethyl)-1,4-naphthoquinone **1** (Ep(1) = - 0.300 V/ SCE) is known as potential bioreductive alkylating agent,[5] there is no study concerning its electron-transfer alkylating properties. Our interest in nitroheterocycles[6] and quinones[2,3] of biological interest led us to investigate the reactivity of **1** in bis-$S_{RN}1$ with nitronates[6b] and a possible way to prepare new highly conjugated naphthoquinones as **4**, good candidates to undergo an electrocyclic ring-closure. The bis-chloride **1** was prepared from naphthoquinone according to Thomson[7] and was reacted with the salt of 2-nitropropane **2** under phase-transfer conditions to give the bis-alkylated derivative **3**.



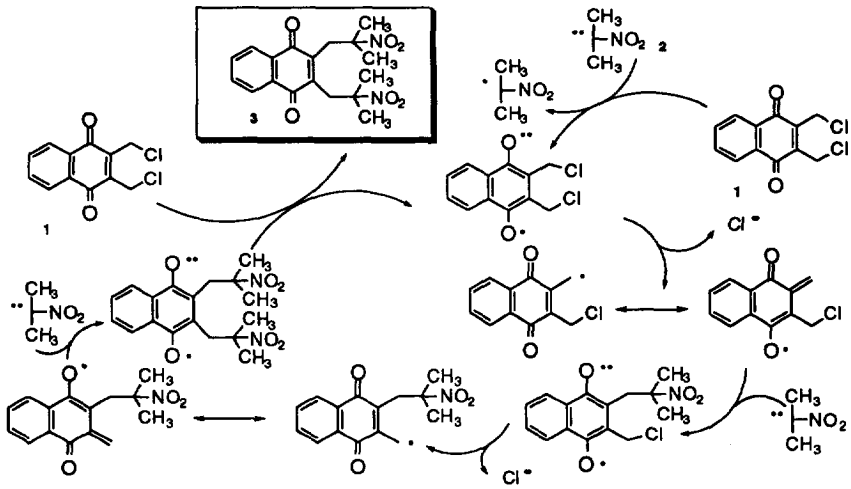
1 **3** **4**

Table. Influence of experimental conditions in the reaction of 1 and 2[a]

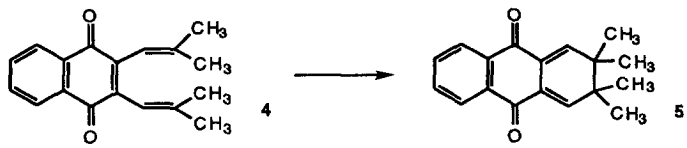
Entry	Scavenger	**3** % Yield
1	-	80
2	p-$NO_2C_6H_4NO_2$ (0.1 eq)	5
3	TEMPO (0.1 eq)	4
4	O_2 (bubbling)	11
5	dark, O_2 (bubbling)	7
6	dark	9

[a]All reactions were performed with 500 mg (1.95 mmol) of **1**, under phase-transfer conditions (dichloromethane-water) by using a **2**/**1** ratio of 5, under nitrogen and irradiation with two 60 W fluorescent lamps; the salt **2** was prepared from 2-nitropropane with NBu_4OH 40% in water.

The reaction of **1** with **2** was studied in the presence of classical inhibitors[8] for establishing the nature of the mechanism. Addition of *p*-dinitrobenzene, TEMPO or bubbling dioxygen through the solution in the dark strongly decrease the yield of **3** indicating that the bis-$S_{RN}1$ mechanism as shown below is most probable.



By treating a solution of **3** (550 mg, 1.5 mmol) in benzene with 6 equiv of NBu_4OH 40% in water at room temperature for 24 h, base-promoted nitrous acid elimination from **3** does not give **4** after work up, but the tricyclic derivative **5**[9] in 33 % yield (not optimized) resulting of an electrocyclic ring-closure.[10]



In conclusion, these results show the first example of a bis-$S_{RN}1$ involving the naphthoquinone system and a rapid way for the preparation of new naphthoquinones just as dihydroanthraquinone derivatives.

References and notes

1. (a) Kornblum, N.; Michel, R. E.; Kerber, R. C. *J. Am. Chem. Soc.* **1966**, *88*, 5660-5662 and 5662-5663. (b) Russell, G. A.; Danen, W. C. *J. Am Chem. Soc.* **1966**, *88*, 5663-5665. (c) Kim, J. K.; Bunnett, J. F. *J. Am Chem. Soc.* **1970**, *92*, 7463-7464.
2. Crozet, M. P.; Jentzer, O.; Vanelle, P. *Tetrahedron Lett.* **1987**, *28*, 5531-5534.
3. Crozet, M. P.; Giraud, L.; Sabuco, J.-F.; Vanelle, P.; Barreau, M. *Tetrahedron Lett.* **1991**, *32*, 4125-4128.
4. Franck, R. W.; Tomasz, M. The Chemistry of Mitomycins. In *The Chemistry of Antitumour Agents*; Vilman, D. E. V. Ed.; Blackie & Son Ltd.: Glasgow, 1990; pp. 379-394.
5. Lin, A. J.; Sartorelli, A. C. *Biochem. Pharmacol.* **1976**, *25*, 206-207 and references therein.
6. (a) Jentzer, O.; Vanelle, P.; Crozet, M. P.; Maldonado, J.; Barreau, M. *Eur. J. Med. Chem.* **1991**, *26*, 687-697. (b) Roubaud, C.; Thèse de Doctorat en Sciences, Université d'Aix-Marseille 3, July 1994. (c) Crozet, M. P.; Gellis, A., Pasquier, C.; Vanelle, P.; Aune, J.-P. *Tetrahedron Lett.* **1995**, *36*, 525-528.
7. Thomson, R. H. *J. Chem. Soc.* **1953**, 1196-1199.
8. Chanon, M.; Tobe, M. L. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 1-23.
9. New derivatives were purified by column chromatography and gave convenient elemental analyses. **3**, yellow solid, mp 151 °C (ethanol), ^1H NMR ($CDCl_3$) δ 1.51 (s, 12H); 3.24 (s, 4H); 7.68 (m, 2H); 8.01 (m, 2H). **5**, yellow solid, mp 92 °C (hexane), ^1H NMR ($CDCl_3$) δ 1.01 (s, 12H); 6.94 (s, 2H); 7.68 (m, 2H); 8.22 (m, 2H). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 21.6 (CH_3); 38.3 (C2, C3); 127.7 (C, CH); 134.0 (CH), 135.8 (C); 149.7 (CH); 181.6 (CO).We thank the referee for the improvement of the manuscript.
10. See for example: Marvell, E. N.; Caple, G.; Schatz, B. *Tetrahedron Lett.* **1965**, 385-389.

(*Received in France* 2 *February* 1996; *accepted* 19 *March* 1996)