Pergamon

Tetrahedron Letters, Vol. 35, No. 20, pp. 3305-3308, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0547-B

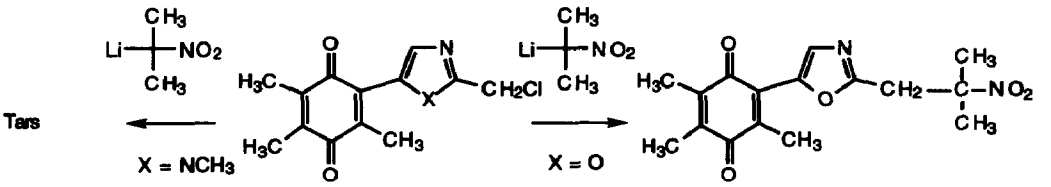
First Electron Transfer C-Alkylation Involving a Fused Quinoneimidazole Reductive Alkylating Agent§

Patrice Vanelle[a]*, Santa Donini[a], José Maldonado[a], Jean-François Sabuco[b] and Michel P. Crozet[c]*

[a]Laboratoire de Chimie Organique, Faculté de Pharmacie, 27 Bd J. Moulin, 13385 Marseille Cedex 05, France
[b]Rhône-Poulenc Rorer, Centre de Recherche de Vitry-Alfortville, 13 Quai Jules-Guesde, BP 14, 94403 Vitry sur Seine Cedex, France
[c]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 C-alkylation reaction of 2-chloromethyl-4,9-dihydro-1-methyl-1H-naphtho[2,3-d]imidazol-4,9-dione by 2-nitropropane anion is shown to proceed by the $S_{RN}1$ mechanism. This mechanism is confirmed by the inhibitory effects of dioxygen, p-dinitrobenzene, cupric chloride and TEMPO.*

In continuation of our program directed toward the study of reductive alkylating agents of potential biological interest in $S_{RN}1$ reactions,[1] we have recently shown the importance of the structure in the difference of reactivity between the quinoneimidazole system and the corresponding oxazole, which can be explained by a steric hindrance to coplanarity of the trimethylquinone and the heterocyclic moieties in the imidazole derivative.[2]

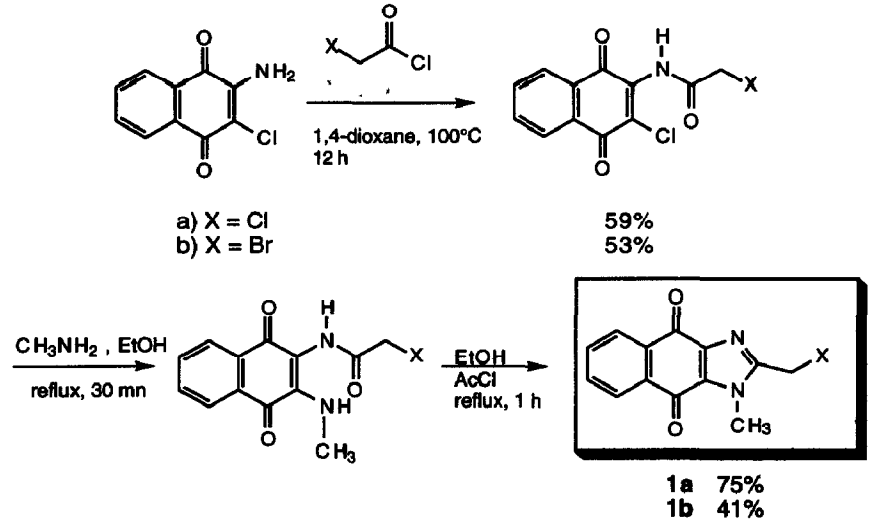


In order to confirm that a quinoneimidazole alkylating agent is able to react by an $S_{RN}1$ mechanism when the quinone and imidazole systems are coplanar, we have synthesized 2-chloromethyl-4,9-dihydro-1-methyl-1H-naphtho[2,3-*d*]imidazol-4,9-dione **1a**[3] and studied its reactivity with 2-nitropropane anion.

The starting material **1a** has been prepared following established procedures[4] in three steps from the inexpensive and commercially available 2-amino-3-chloro-1,4-naphthoquinone as shown in Scheme 1.
To study the influence of the leaving group, the bromide **1b** has been obtained by replacing chloroacetyl chloride by the corresponding bromide and the acetoxymethyl derivative **1c** by treating **1a** by sodium acetate and a catalytic amount of TBAB in dichloromethane.

§This paper is dedicated to the memory of Professor Nathan Kornblum.

Scheme 1



The derivative **1a-c** reacts with lithium salt of 2-nitropropane **2** under Kornblum conditions[5] (degassed DMF, inert atmosphere and photostimulation) and gives the ethylenic derivative **4**[6] formed from the C-alkylation product **3** by base-promoted nitrous acid elimination (Scheme 2). Various experimental conditions reported in the Table have been studied to establish the mechanism.

Scheme 2

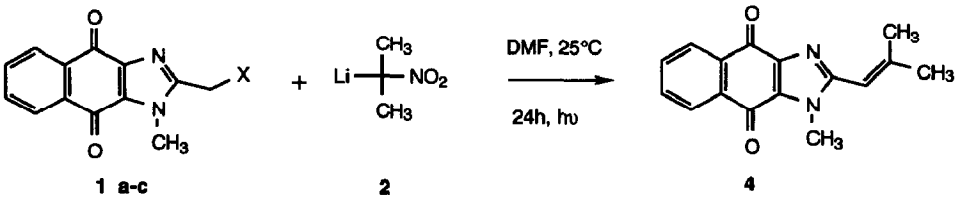


Table Influence of experimental conditions in the reaction of **1a-c** and **2**[a].

Entry	Mol. equiv. of **2**	X	Scavenger (mol. equiv.)	**4** % yield
1	1	Cl	-	9
2	2	Cl	-	47
3	3	Cl	-	58
4	4	Cl	-	79
5	3	Cl	$CuCl_2$ (0.1)	traces
6	3	Cl	dark, O_2 (bubbling)	14
7	3	Cl	TEMPO[b] (0.1)	2
8	3	Cl	p-$NO_2C_6H_4NO_2$ (1)	10
9	3	Br	-	24
10	3	$OCOCH_3$	-	4

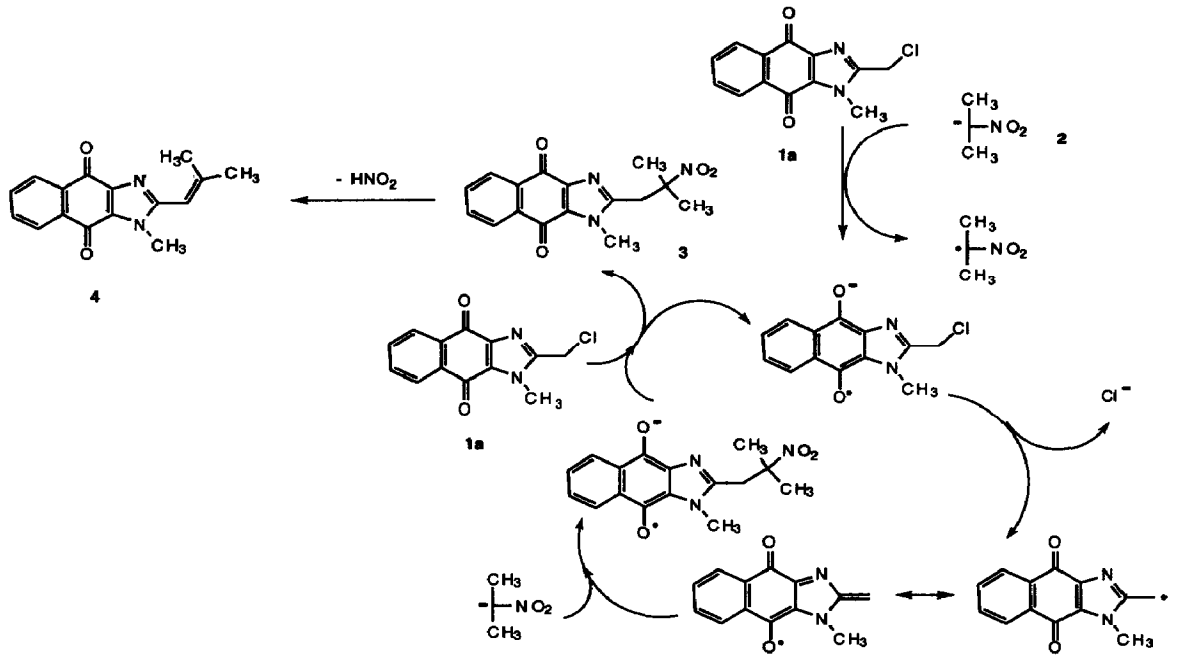
[a]All reactions were performed unless otherwise noted during 24h by using one equivalent of **1** under nitrogen and irradiation with two 60W fluorescent lamps. [b]2,2,6,6-tetramethyl-1-piperidinyloxy.

The results of the Table show the important role played by the ratio of the nucleophile to the substrate concentration. The best C-alkylation yield is obtained when 4 equivalents of 2-nitropropane anion are used under Kornblum conditions. This factor has been precedently demonstrated in $S_{RN}1$ aromatic substitutions,[7] and we have shown in nitroimidazole[8] and nitrothiophene[9] series that the use of an excess of the nitronate anion increased the yield of C-alkylation. Inspection of the Table also reveals the influence of the nature of the leaving group. When X is Br (derivative **1b**), the formation of **4** is significantly decreased as observed by Kornblum[10] with *p*-nitrobenzyl halides. The decrease in the C-alkylation yield is notably stronger with **1c** (X = $OCOCH_3$) as proposed by Blankespoor[11] in 9,10-anthraquinone series.

To demonstrate the operation of an $S_{RN}1$ mechanism, we have used classical inhibition experiments[12] such as reaction in the dark, electron trapping and radical scavengers. The addition of cupric chloride or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) in catalytic quantities completely inhibits the chain reaction (entries 5, 7). When bubbling dioxygen in the dark (entry 6) or by addition of a stoichiometric quantity of *p*-dinitrobenzene (entry 8), the formation of **4** strongly decreases.

All these experimental data provide good evidence for assigning the $S_{RN}1$ mechanism to the reaction of 2-chloromethyl-4,9-dihydro-1-methyl-1H-naphtho[2,3-*d*]-imidazol-4,9-dione **1a** and 2-nitropropane anion **2**. This mechanism is illustrated by the following classical chain process (Scheme 3).

Scheme 3



In conclusion, these results show that the reductive alkylating agent **1**, in which the quinone is coplanar with the imidazole bearing the leaving group, reacts with the 2-nitropropane anion **2** to give C-alkylation by the $S_{RN}1$ mechanism. It is the first example of an $S_{RN}1$ reaction involving a fused quinoneimidazole system and a new way for the preparation of naphthoimidazolediones bearing a trisubstituted double bond at 2-position. The derivative **4** showing interesting antiprotozoan activity;[13] the extension of this reaction to heterocyclic nitronate anions and the pharmacological studies of the resulting 2-substituted new fused quinone-imidazoles are in progress.

ACKNOWLEDGEMENT

The support of this work by the Centre National de la Recherche Scientifique is gratefully acknowledged. We express our thanks to Dr. Michel Barreau for helpful discussions and the Département Biologie of the Centre de Recherche at Vitry-Alfortville of Rhône-Poulenc Rorer for biological studies.

REFERENCES AND NOTES

1. (a) Vanelle, P.; Crozet, M. P.; Maldonado, J.; Barreau, M. *Eur. J. Med. Chem.* **1991**, *26*, 167-178. (b) Jentzer, O.; Vanelle, P.; Crozet, M. P.; Maldonado, J.; Barreau, M. *Eur. J. Med. Chem.* **1991**, *26*, 687-697. (c) Crozet, M. P.; Giraud, L.; Sabuco, J.-F.; Vanelle, P.; Barreau, M. *Tetrahedron Lett.* **1991**, *32*, 4125-4128. (d) Crozet, M. P.; Vanelle, P.; Jentzer, O.; Donini, S.; Maldonado, J. *Tetrahedron*, **1993**, *49*, 11253-11262.
2. (a) Sabuco, J.-F. *Thesis*, 1991, University of Aix-Marseille. (b) Crozet, M. P.; Sabuco, J.-F.; Tamburlin, I.; Barreau, M.; Giraud, L.; Vanelle, P. *Heterocycles* , **1993**, *36*, 45-54.
3. For studies of related heterocyclic reductive agents as cancer drugs, see: (a) Boruah, R. C.; Skibo, E. B. *J. Org. Chem.* **1993**, *58*, 7797-7803. (b) Skibo, E. B.; Islam, I.; Heileman, M. J.; Schulz, W. G. *J. Med. Chem.* **1994**, *37*, 78-92 and references therein.
4. Kallmayer, H.-J.; Binger, M. *Pharmazie* , **1990**, *45*, 184-186.
5 Kornblum, N.; Michel, R. E.; Kerber, R. C. *J. Am Chem. Soc.* **1966**, *88*, 5662-5663.
6. All derivatives have been isolated as pure products and fully characterized: **1a**, yellow solid, mp 210 °C (ethanol), ^{1}H NMR ($CDCl_3$) δ 4.19 (s, 3H), 4.81 (s, 2H), 7.76 (m, 2H); 8.18 (m, 1H); 8.26 (m, 1H). **1b**, red solid, mp 214 °C (ethanol), ^{1}H NMR ($CDCl_3$) δ 4.18 (s, 3H), 4.80 (s, 2H), 7.76 (m, 2H); 8.17 (m, 1H); 8.26 (m, 1H). **1c**, yellow solid, mp 176 °C (ethanol), ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3H), 4.14 (s, 3H), 5.32 (s, 2H), 7.76 (m, 2H); 8.16 (m, 1H); 8.26 (m, 1H). **4**, yellow solid, mp 210 °C (methanol), ^{1}H NMR ($CDCl_3$) δ 2.06 (s, 3H), 2.30 (s, 3H), 4.04 (s, 3H), 6.09 (s, 1H), 7.71 (m, 2H); 8.14 (m, 1H); 8.24 (m, 1H).
7 Amatore, C.; Pinson, J.; Savéant, J.-M.; Thiébault, A. *J. Am Chem. Soc.* **1981**, *103*, 6930-6937.
8 Vanelle, P. *Thesis*, 1987, University of Aix-Marseille.
9 Vanelle, P.; Ghezali, S.; Maldonado, J.; Crozet, M. P.; Delmas, F.; Gasquet, M.; Timon-David, P. *Eur. J. Med. Chem.* **1994**, *29*, 41-44.
10 Kornblum, N.; Pink, P.; Yorka, K. V. *J. Am Chem. Soc.* **1961**, *83*, 2779-2780.
11 (a) Blankespoor, R. L.; Schutt, D. L.; Tubergen, M. B.; De Jong, R. L. *J. Org. Chem.* **1987**, *52*, 2059-2064. (b) Blankespoor, R. L.; Hsung, R. J.; Schutt, D. L. *J. Org. Chem.* **1988**, *53*, 3032-3035.
12 Chanon, M.; Tobe, M. L. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 1-23.
13 Part of these results was presented at the XXVIIIièmes Rencontres Internationales de Chimie Thérapeutique, 7-9 July 1992, Toulouse, France.

(*Received in France* 8 *February* 1994; *accepted* 17 *March* 1994)