

COMPETITION BETWEEN C- AND O-ALKYLATION REACTIONS IN 5-NITROIMIDAZOLE SERIES: INFLUENCE OF NUCLEOPHILE

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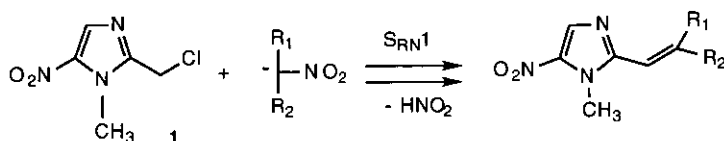
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Abstract- The new reductive alkylating agent, 2-(4-chloromethylstyryl)-1-methyl-5-nitro-1*H*-imidazole gives exclusively *O*-alkylation with 2-nitropropane anion. The electron-transfer *C*-alkylation is observed with the anions of ethyl 2-nitropropionate and dialkyl α -substituted malonates. The competition between *C*- and *O*-alkylation reactions depends on the nature of the nucleophile because of the low rate of decomposition of the radical anion of the alkylating agent.

The nitroimidazoles are valuable drugs for the treatment of several protozoal diseases as well as infections due to anaerobic bacteria and for the radiosensitization of hypoxic tumors.¹ However, resistance to these compounds has been demonstrated in trichomonads and *Bacteroides fragilis*.² Moreover, some 5-nitroimidazoles have been found to be mutagenic and carcinogenic.³ Thus, new principles for treatment of infections are therefore highly desirable.

We have previously demonstrated that 1-methyl-2-chloromethyl-5-nitro-1*H*-imidazole (**1**) reacted with nitronate anions through $S_{RN}1$ mechanism.⁴ Thus, a new class of 5-nitroimidazoles bearing a tri-substituted double bond at 2-position was obtained after nitrous acid elimination (Scheme 1).

Scheme 1

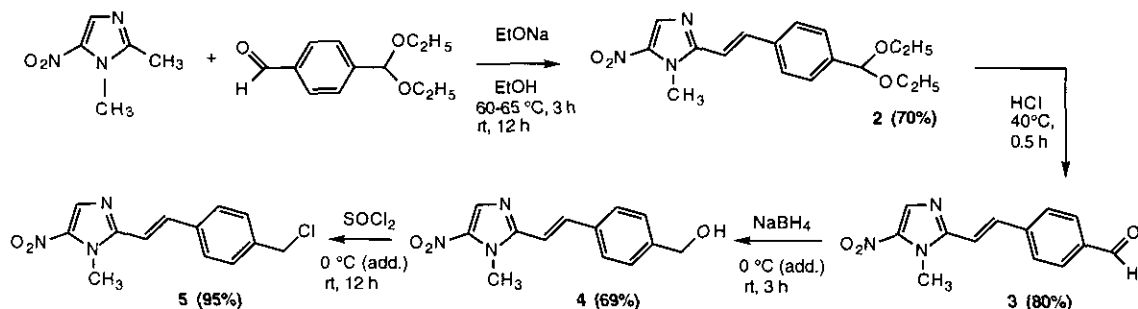


The structure-activity relationship studies have revealed an increase of conjugation in the molecular structures of the most potent antimicrobial and antiparasitic compounds.⁵ In order to increase the conjugated system and to develop more active analogues, we have synthesized the new reductive alkylating agent, 2-(4-chloromethylstyryl)-1-methyl-5-nitro-1*H*-imidazole (**5**) and studied its reactivity in a classical

electron-transfer C -alkylation reaction. In addition, **5** appeared to be a good candidate to investigate new $S_{RN}1$ reactions involving a long distance (ten bonds) between the electron-withdrawing and leaving groups. We propose the term LD- $S_{RN}1$ or Long Distance- $S_{RN}1$ for these reactions.

The starting material (**5**) has been prepared in four steps by base-catalyzed condensation of 1,2-dimethyl-5-nitro-1*H*-imidazole (dimetridazole) with 4-diethoxymethylbenzaldehyde, deprotection,⁶ reduction and chlorination as shown in Scheme 2.

Scheme 2



The chloride (**5**) reacts with 2-nitropropane (**6**) under different appropriate conditions for $S_{RN}1$ reactions (inert atmosphere, light) as shown in Scheme 3. The results are summarized in Table 1.

Scheme 3

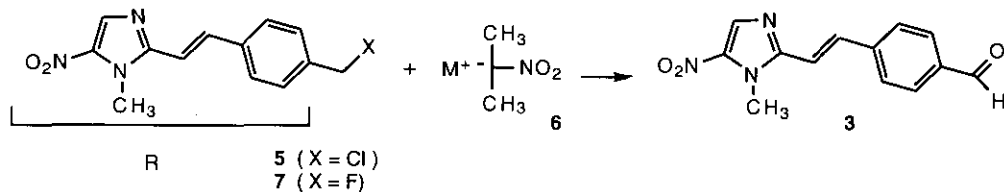


Table 1

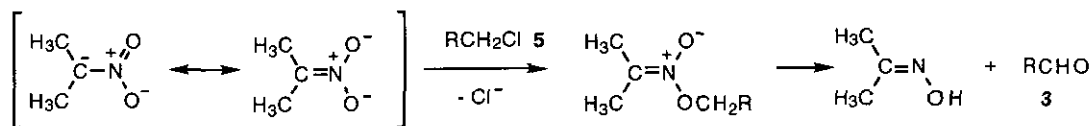
Influence of experimental conditions in the reaction of **5** with **6**^a

Entry	M	Solvent	T (°C)	Time (h)	3	5 ^e Yield %
1	Li	DMF	25	12	90	-
2	Li	DMF	0	24	15	75
3	Li	DMF	-20	24	4	88
4	Li	DMF ^b	25	24	35	55
5	N(C ₄ H ₉) ₄	CH ₂ Cl ₂ -H ₂ O ^c	25	12	86	-
6	N(C ₄ H ₉) ₄	C ₆ H ₅ CH ₃ -H ₂ O ^c	25	12	72	-
7	N(C ₄ H ₉) ₄	C ₆ H ₅ CH ₃ -H ₂ O ^d	25	12	-	95

^aAll reactions were performed with **5** (1 eq.) and **6** (3 eq.), under nitrogen and irradiation with two 60 W tungsten lamps. ^bCatalysis by FeBr₂ (0.71 eq.). ^cPhase-transfer conditions with 40% N(C₄H₉)₄OH in water. ^dPhase-transfer catalysis with N(C₄H₉)₄Br (0.1 eq.). ^eRecovered product.

The results reported in Table 1 show that **5** reacts with the anion of **6** to give exclusively **3** with the best yield (90%) obtained under the usual conditions described by Kornblum with DMF as solvent. An S_N2 process leads to the unstable nitronic ester which breaks down into an oxime (not isolated under the reaction conditions) and the aldehyde (**3**) as described in Scheme 4.⁷

Scheme 4



Contrary to precedent results with **1**⁴ or with *p*-nitrobenzyl chloride,^{7,8} the S_N2 displacement is so fast that the electron-transfer chain process does not compete effectively in the case of the conjugated chloride (**5**). Even when the reaction was induced by FeBr_2 , an efficient reagent to facilitate initiation of $S_{RN}1$ reaction,⁹ **3** was also obtained. As our group has recently reported the displacement of a fluoride by $S_{RN}1$ reaction at sp^3 carbon in quinonic series,¹⁰ we have studied the influence of leaving group in the reaction of **5** with **6**. The fluoro compound (**7**) was prepared in 95% yield from **4** following Middleton method¹¹ with diethylaminosulfur trifluoride (DAST) and was recovered unchanged after reacting with **6** under various reaction conditions as used in the Entries 1, 4, 5, and 7 in Table 1.

The formation of **3** was unexpected because **5** and **1** show very similar cyclic voltammograms with $E_{p1} = -1120$ mV vs SCE against -1040 mV.¹² Indeed, from these electrochemical data, **5** appeared to be a convenient substrate for $S_{RN}1$ reaction.

As the nature of nucleophile is crucial to $S_{RN}1$ reactions, an understanding of the relationship between the nucleophile and the substrate in single electron transfer is of use to increase the selectivity and the yield of the reaction.¹³ Thus, we have used other conventional nucleophiles in $S_{RN}1$ reaction. Replacement of **6** by nitrocyclohexane in the experimental conditions of Entry 1 in Table 1 gave **3** again in 55% yield. We have recently shown that anion of ethyl 2-nitropropionate (**8**) reacted with *p*-nitrobenzyl chloride and **1** to give the *C*-alkylation derivatives (79% and 70% yields) by $S_{RN}1$ mechanism.¹⁴ The sodium salt of **8**, prepared from ethyl 2-nitropropionate with sodium hydride in DMSO, reacted with the chloride (**5**) at room temperature to give a mixture of *C*- and *O*-alkylation derivatives as demonstrated in Scheme 5. The results are summarized in Table 2.

Scheme 5

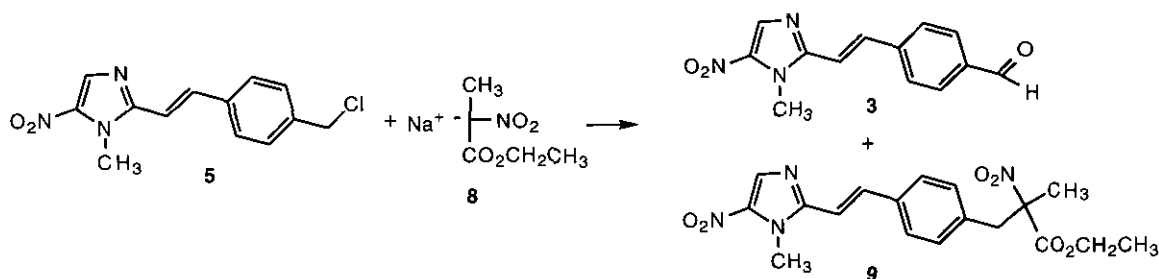


Table 2

Influence of experimental conditions in the reaction of **5** with **8** to give the products (**3**) and (**9**)^a

Entry	Solvent	Scavenger (mol. equiv.)	Time (h)	5 ^b	9	3 Yield%
9	DMSO	-	24	45	30	20
10	DMSO	-	36	-	55	35
11	DMSO	O ₂ (bubbling)	36	-	15	48
12	DMSO	dark	36	-	5	53
13	DMSO	dark, O ₂ (bubbling)	36	-	-	60
14	DMSO	TEMPO (1)	36	-	-	38
15	DMSO	<i>p</i> -NO ₂ C ₆ H ₄ NO ₂ (1)	36	-	-	41
16	DMSO	CuCl ₂ (1)	36	5	-	55

^aAll reactions were performed with **5** (1 eq.) and **8** (3 eq.), under nitrogen and irradiation with two 60 W tungsten lamps. ^bRecovered product.

Total inhibition for the production of **9** (Table 2) was observed with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), *p*-dinitrobenzene, cupric chloride in stoichiometric quantities or when bubbling dioxygen in the dark. Only the *O*-alkylation product (**3**) was formed in 38-60% yields. The effects of classical inhibitors¹⁵ on the reaction of **5** with **8** leading to **9** provide good evidence for assigning the S_{RN}1 mechanism for the *C*-alkylation. As malonates are known as classical nucleophiles for S_{RN}1 reactions,¹⁶ we have investigated the reactivity of diethyl phenylmalonate (**10a**) or dimethyl bromomalonate (**10b**) anions with **5**. The results are summarized in Table 3.

Table 3

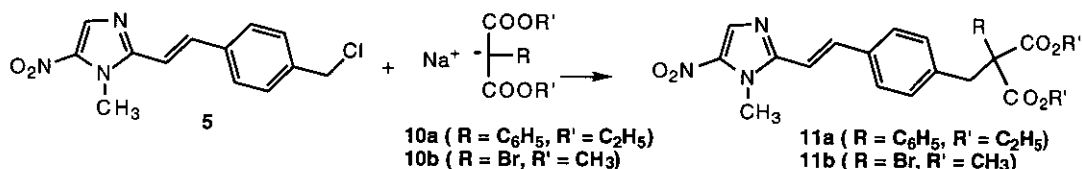
Influence of experimental conditions in the reaction of **5** with **10** to give the products (**11**)^a

Entry	Anion	Solvent	Scavenger (mol. equiv.)	Yield% 11a	11b
17	10a	DMSO	-	85	
18	10a	DMSO	O ₂ (bubbling)	9	
19	10a	DMSO	dark	6	
20	10a	DMSO	dark, O ₂ (bubbling)	traces	
21	10a	DMSO	TEMPO (1)	49	
22	10a	DMSO	<i>p</i> -NO ₂ C ₆ H ₄ NO ₂ (1)	25	
23	10a	DMSO	CuCl ₂ (1)	20	
24	10b	DMSO	-		90
25	10b	DMSO	O ₂ (bubbling)		11
26	10b	DMSO	dark		8
27	10b	DMSO	dark, O ₂ (bubbling)		traces
28	10b	DMSO	TEMPO (1)		46
29	10b	DMSO	<i>p</i> -NO ₂ C ₆ H ₄ NO ₂ (1)		29
30	10b	DMSO	CuCl ₂ (1)		20

^aAll reactions were performed with **5** (1 eq.) and **10** (3 eq.), under nitrogen and irradiation with two 60 W tungsten lamps, during 24 h and at rt.

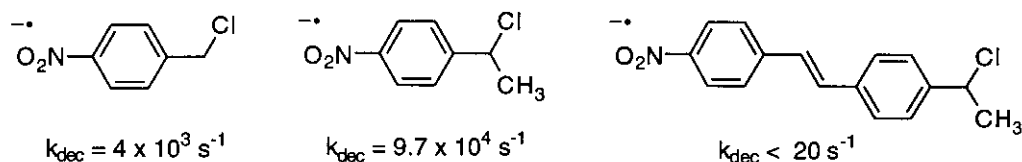
The results reported in Table 3 show that **5** reacted with the anions of **10a** and **10b** to give the expected *C*-alkylation products (**11**) in excellent yield (85 to 90%) under Kornblum conditions, as shown in Scheme 6.

Scheme 6



The *C*-alkylation was partially inhibited in presence of inhibitors (Table 3). By addition of a stoichiometric quantity of TEMPO, *p*-dinitrobenzene or cupric chloride, the formation of **11** significantly decreased. The bubbling dioxygen in the dark completely inhibited the *C*-alkylation reaction.

It has been previously reported that the balance between the two competitive *C*- and *O*-alkylation reactions with ambident nitronate anions depends on the alkylating agent (position and presence of the nitro group^{7,8} and nature of the leaving group^{7,8}), the basicity of the anions¹⁷ and the rate of decomposition of the radical anion of the alkylating agent.¹⁸ The rate constant for the decomposition of the radical anion of **5** was estimated to be around 500 s⁻¹ from electrochemical studies.¹⁹ This rate constant is very low compared to the rate constant for the decomposition of the radical anions of *p*-nitrobenzyl chlorides but higher than the rate constant for the decomposition of the radical anion of the stilbene analogue of **5** as shown below.



If the rate of decomposition of the radical anion of **5** is very slow, the S_{RN}1 becomes a very slow process. The chloride (**5**) undergoes S_N2 rather than S_{RN}1 with 2-nitropropane anion, whereas the S_N2 becomes a slow process with a less powerful nucleophile such as ethyl 2-nitropropionate anion. Thus, the competing S_{RN}1 becomes possible. The anions of diethyl phenylmalonate and dimethyl bromomalonate (**10a**) and (**10b**) react by S_{RN}1 and S_N2 to give the *C*-alkylation derivatives. If the S_{RN}1 is inhibited, the *C*-alkylation derivatives can be formed by S_N2.

In conclusion, we have shown that **5**, a new reductive alkylating agent, gives exclusively the aldehyde (**3**) by *O*-alkylation reaction with 2-nitropropane anion. However, **5** gives a mixture of a *C*-alkylation product (**9**) and an *O*-alkylation product (**3**) with a less powerful nucleophile such as ethyl 2-nitropropionate anion. Therefore, the nature of the nucleophile and the conjugated system between the acceptor and the leaving groups of a reductive alkylating agent are very important on the course of the S_{RN}1 reaction. This electron-transfer *C*-alkylation of **5** is the first example of a LD-S_{RN}1 mechanism in 5-nitroimidazole series. These results open the way for the synthesis of highly conjugated 5-nitroimidazoles from **5**.

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EXPERIMENTAL

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Bruker 200 MHz instrument and chemical shifts are reported in δ units (ppm) relative to internal TMS. Microanalyses were performed by the Microanalytical Section of St-Jérôme Faculty, Aix-Marseille 3 University, France.

2-(4-Diethoxymethylstyryl)-1-methyl-5-nitro-1H-imidazole (2)

Sodium (0.55 g, 0.024 g atom) was stirred in absolute ethanol (25 mL) until complete dissolution and 1,2-dimethyl-5-nitro-1H-imidazole (1.41 g, 10 mmol) and 4-diethoxymethylbenzaldehyde (3.65 g, 17.5 mmol) were added. After stirring at 60–65 °C for 3 h, the reaction mixture was cooled and stirred at rt for 12 h. The obtained precipitate was filtered, washed with ethanol, water and absolute ethanol. After purification by recrystallization from ethanol, **2** was obtained as yellow solid (2.32 g, 70%). mp 74–75 °C, ^1H NMR (CDCl_3) δ 1.22 (m, 6H); 3.56 (m, 4H); 4.00 (s, 3H); 5.50 (s, 1H); 6.86 (d, J = 15.7 Hz, 1H); 7.51 (m, 4H); 7.85 (d, J = 15.7 Hz, 1H); 8.04 (s, 1H). Anal. Calcd for $\text{C}_{17}\text{H}_{21}\text{N}_3\text{O}_4$: C, 61.62; H, 6.39; N, 12.68. Found: C, 61.70; H, 6.50; N, 12.60.

4-[2-(1-Methyl-5-nitro-1H-imidazol-2-yl)vinyl]benzaldehyde (3)

To a solution of **2** (2.32 g, 7 mmol) in tetrahydrofuran (THF, 30 mL), were added water (10 mL) and 37% hydrochloric acid (5 mL). The reaction mixture was stirred at 40 °C for 30 min. After cooling, the residue was filtered and purified by recrystallization from ethanol to give 1.44 g (80%) of yellow solid. **3**, mp 180 °C, ^1H NMR (CDCl_3) δ 4.09 (s, 3H); 7.03 (d, J = 15.7 Hz, 1H); 7.72 (d, J = 8.3 Hz, 2H); 7.92 (d, J = 8.3 Hz, 2H); 8.01 (d, J = 15.7 Hz, 1H); 8.10 (s, 1H); 10.03 (s, 1H). Anal. Calcd for $\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_3$: C, 60.68; H, 4.31; N, 16.34. Found: C, 60.70; H, 4.25; N, 16.25.

{4-[2-(1-Methyl-5-nitro-1H-imidazol-2-yl)vinyl]phenyl}methanol (4)

To a solution of **3** (1.44 g, 5.6 mmol) in dry THF (50 mL), was added slowly sodium borohydride (0.635 g, 17 mmol) at 0 °C. After stirring at rt for 3 h, the reaction mixture was poured into water (100 mL), extracted with dichloromethane and dried over anhydrous magnesium sulfate. The solvent was evaporated under vacuum. The extract was purified by chromatography on a silica gel column eluting with dichloromethane-acetone (9:1) and recrystallization of the eluate from cyclohexane to give 1 g (69%) of yellow solid. **4**, mp 214 °C, ^1H NMR (CDCl_3) δ 4.06 (s, 3H); 4.74 (s, 2H); 6.89 (d, J = 15.7 Hz, 1H); 7.41 (d, J = 8.2 Hz, 2H); 7.57 (d, J = 8.2 Hz, 2H); 7.88 (d, J = 15.7 Hz, 1H); 8.10 (s, 1H). Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_3$: C, 60.23; H, 5.05; N, 16.21. Found: C, 60.40; H, 4.95; N, 16.19.

2-(4-Chloromethylstyryl)-1-methyl-5-nitro-1H-imidazole (5)

Thionyl chloride (1.37 g, 11.55 mmol) was added dropwise at 0 °C to a solution of **4** (1 g, 3.85 mmol) in dry dichloromethane (30 mL) in a round-bottomed flask equipped with a reflux condenser surmounted by a calcium chloride drying tube. After stirring at rt for 12 h, the reaction mixture was evaporated under reduced pressure. The residue was dissolved in water. The aqueous solution was then basified with saturated sodium bicarbonate solution. Extraction with dichloromethane, drying of the extracts over anhydrous magnesium sulfate, removal of the solvent under reduced pressure and recrystallization of the

product from ethanol gave 1.02 g (95%) of yellow solid. **5**, mp 268-270 °C, ^1H NMR (CDCl_3) δ 4.05 (s, 3H); 4.60 (s, 2H); 7.00 (d, $J = 15.7$ Hz, 1H); 7.42 (d, $J = 8.2$ Hz, 2H); 7.57 (d, $J = 8.2$ Hz, 2H); 7.87 (d, $J = 15.7$ Hz, 1H); 8.02 (s, 1H). ^{13}C NMR (CDCl_3) δ 32.77; 45.66; 111.77; 127.73; 129.18; 134.16; 135.28; 138.81; 138.96; 149.54. Anal. Calcd for $\text{C}_{13}\text{H}_{12}\text{N}_3\text{O}_2\text{Cl}$: C, 56.23; H, 4.36; N, 15.13; Cl, 12.77. Found: C, 56.20; H, 4.30; N, 15.15; Cl, 12.80.

2-(4-Fluoromethylstyryl)-1-methyl-5-nitro-1H-imidazole (7)

A solution of **4** (2 g, 7.71 mmol) in dry dichloromethane (30 mL) was added dropwise to a cooled (-78°C) and stirred solution of diethylaminosulfur trifluoride (DAST) (3.72 g, 23.1 mmol) in dry dichloromethane (20 mL). The reaction mixture was allowed to warm up to rt, washed with water, dried over magnesium sulfate and evaporated under reduced pressure. Purification by chromatography on a silica gel column eluting with dichloromethane and recrystallization from ethanol gave 1.91 g (95%) of yellow solid. **7**, mp 220°C , ^1H NMR (CDCl_3) δ 4.07 (s, 3H); 5.41 (d, $J_{\text{H,F}} = 47$ Hz, 2H); 6.91 (d, $J = 15.7$ Hz, 1H); 7.42 (d, $J = 8.8$ Hz, 2H); 7.60 (d, $J = 8.8$ Hz, 2H); 7.88 (d, $J = 15.7$ Hz, 1H); 8.09 (s, 1H). Anal. Calcd for $\text{C}_{13}\text{H}_{12}\text{N}_3\text{O}_2\text{F}$: C, 59.77; H, 4.63; N, 16.08. Found: C, 59.81; H, 4.70; N, 16.00.

General procedure for the reactions with nitronate anions

The lithium salt of 2-nitropropane (**6**) or nitrocyclohexane was prepared as previously described.²⁰ Ethyl 2-nitropropionate (**8**) was prepared from commercial ethyl 2-bromopropionate.¹⁴

* Kornblum conditions (Entry 1 in Table 1)

To a solution of 0.20 g (0.72 mmol) of **5** in dry DMF (10 mL), 0.20 g (2.16 mmol) of lithium salt of 2-nitropropane was added under dry nitrogen. The reaction mixture was then irradiated with two 60W fluorescent lamps from a distance of 10 cm. After stirring at rt for 12 h, the reaction mixture was poured into water (100 mL). The aqueous solution was extracted with benzene (3 x 20 mL) and ether (1 x 20 mL). The organic extracts were combined and washed with water (3 x 50 mL), dried over magnesium sulfate and evaporated under reduced pressure. Purification by chromatography on silica column eluting with dichloromethane gave 0.167 g (90%) of **3**.

* Norris conditions (Entry 5 in Table 1)

Under nitrogen atmosphere, an aqueous solution of 40% tetrabutylammonium hydroxide in water (1.4 g, 2.16 mmol) reacted with 2-nitropropane (0.19 g, 2.16 mmol) for 1 h. A solution of **5** (0.20 g, 0.72 mmol) in dichloromethane (10 mL) was added and the mixture was stirred for 12 h under irradiation with fluorescent lamps. The organic layer was separated and the aqueous layer was extracted with three portions of dichloromethane (10 mL). The combined organic layers were removed under reduced pressure. The residue was dissolved in benzene (20 mL), washed twice with water (20 mL), dried over magnesium sulfate and evaporated. The purification gave **3** (0.16 g, 86%).

General procedure for the reactions with ethyl 2-nitropropionate (Entry 9 in Table 2) or malonate anions (Entries 17 and 24 in Table 3)

Sodium hydride (dry, 95%, 0.055 g, 2.16 mmol) was stirred in dry dimethyl sulfoxide (DMSO, 5 mL) until complete dissolution and a solution of ethyl 2-nitropropionate (0.32 g, 2.16 mmol) or diethyl phenylmalonate (0.51 g, 2.16 mmol) or dimethyl bromomalonate (0.46 g, 2.16 mmol) in DMSO (5 mL) was quickly added. The reaction mixture was stirred at reflux for 30 min. A solution of **5** (0.2 g, 0.72 mmol) in DMSO (5 mL) was added for 45 min and the mixture was stirred for 24 h under nitrogen and irradiation with fluorescent lamps. The reaction mixture was poured into water (100 mL). The aqueous

solution was extracted with dichloromethane (3 x 20 mL). The organic extracts were washed with water (3 x 50 mL), dried over magnesium sulfate and evaporated under reduced pressure. Purification by chromatography on a silica gel column eluting with dichloromethane gave the following products.

2-Methyl-3-{4-[2-(1-methyl-5-nitro-1H-imidazol-2-yl)vinyl]phenyl}-2-nitro propionic acid ethyl ester (9)

30% yield (84 mg), mp 115 °C (hexane), ^1H NMR (DMSO- d_6) δ 1.20 (t, J = 7.1 Hz, 3H); 1.66 (s, 3H); 3.51 (AB type, J_{AB} = 13.7 Hz, $\Delta\nu$ = 35.65 Hz, 2H); 4.02 (s, 3H); 4.25 (q, J = 7.1 Hz, 2H); 7.21 (d, J = 7.9 Hz, 2H); 7.40 (d, J = 15.8 Hz, 1H); 7.73 (d, J = 7.9 Hz, 2H); 7.80 (d, J = 15.8 Hz, 1H); 8.24 (s, 1H). ^{13}C NMR (CDCl_3) δ 13.65; 20.36; 32.99; 40.74; 62.90; 93.07; 113.07; 127.90; 130.72; 133.42; 134.71; 134.86; 137.87; 139.10; 149.42; 166.69. Anal. Calcd for $\text{C}_{18}\text{H}_{20}\text{N}_4\text{O}_6$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.73; H, 5.26; N, 14.50.

2-{4-[2-(1-Methyl-5-nitro-1H-imidazol-2-yl)vinyl]benzyl}-2-phenylmalonic acid diethyl ester (11a)

85% yield (292 mg), mp 142 °C (hexane), ^1H NMR (CDCl_3) δ 1.20 (t, J = 7.1 Hz, 6H); 3.61 (s, 2H); 4.01 (s, 3H); 4.19 (q, J = 7.1 Hz, 4H); 6.80 (d, J = 15.7 Hz, 1H); 6.92 (d, J = 8.2 Hz, 2H); 7.25 (m, 5H); 7.34 (d, J = 8.2 Hz, 2H); 7.79 (d, J = 15.7 Hz, 1H); 8.05 (s, 1H). Anal. Calcd for $\text{C}_{26}\text{H}_{27}\text{N}_3\text{O}_6$: C, 65.40; H, 5.70; N, 8.80. Found: C, 65.51; H, 5.65; N, 8.89.

2-Bromo-2-{4-[2-(1-methyl-5-nitro-1H-imidazol-2-yl)vinyl]benzyl}malonic acid dimethyl ester (11b)

90% yield (293 mg), mp 160 °C (hexane), ^1H NMR (CDCl_3) δ 3.86 (s, 6H); 4.06 (s, 3H); 4.60 (s, 2H); 6.90 (d, J = 15.7 Hz, 1H); 7.43 (d, J = 8.2 Hz, 2H); 7.57 (d, J = 8.2 Hz, 2H); 7.87 (d, J = 15.7 Hz, 1H); 8.09 (s, 1H). ^{13}C NMR (CDCl_3) δ 32.70; 45.61; 53.38; 118.64; 127.70; 127.76; 129.13; 129.61; 134.07; 135.32; 138.74; 138.94; 149.54; 162.54. Anal. Calcd for $\text{C}_{18}\text{H}_{18}\text{N}_3\text{O}_6\text{Br}$: C, 47.80; H, 4.01; N, 9.29. Found: C, 47.90; H, 3.95; N, 9.36.

Inhibition studies with *p*-dinitrobenzene, cupric chloride and TEMPO were carried out by adding the required amount of *p*-dinitrobenzene, cupric chloride and TEMPO to the reaction mixture immediately prior to the chloride (5). The study in the dark was obtained by wrapping the flask in aluminum foil. Inhibition study with molecular oxygen was carried out by replacing nitrogen by oxygen. The results of these respective studies are shown in Tables 2 and 3.

REFERENCES

1. A. Breccia, B. Cavalerri, and G. E. Adams, 'Nitroimidazoles: Chemistry, Pharmacology and Clinical Application,' Plenum Press, New York, 1982; M. D. Nair and K. Nagarajan, 'Progress in Drug Research: Nitroimidazoles as chemotherapeutic agents,' Vol. 27, ed. by E. Jucker, Birkhauser Verlag, Basel, 1983, pp. 163-252.
2. J. G. Meingassner, H. Mieth, R. Czok, D. G. Lindmark, and M. Muller, *Antimicrob. Agents Chemother.*, 1978, **13**, 1; M. L. Britz and R. G. Wilkinson, *ibid.*, 1979, **16**, 19.
3. C. E. Voogd, *Mutat. Res.*, 1981, **86**, 243; M. De M  o, P. Vanelle, E. Bernadini, M. Laget, J.

- Maldonado, O. Jentzer, M. P. Crozet, and G. Duménil, *Env. Mol. Mutagen.*, 1992, **19**, 167; J. L. Ré, M. De Méo, M. Laget, H. Guiraud, M. Castegnaro, P. Vanelle, and G. Duménil, *Mutat. Res.*, 1997, **375**, 147.
4. M. P. Crozet, J.-M. Surzur, P. Vanelle, C. Ghiglione, and J. Maldonado, *Tetrahedron Lett.*, 1985, **26**, 1023.
 5. L. Bouscasse, D. Bouin, M. P. Crozet, O. Jentzer, and P. Vanelle, *Spectrosc. Lett.*, 1989, **22**, 693; P. Vanelle, M. P. Crozet, J. Maldonado, and M. Barreau, *Eur. J. Med. Chem.*, 1991, **26**, 167; O. Jentzer, P. Vanelle, M. P. Crozet, J. Maldonado, and M. Barreau, *ibid.*, 1991, **26**, 687; P. Vanelle, J. Maldonado, M. Gasquet, F. Delmas, P. Timon-David, O. Jentzer, and M. P. Crozet, *J. Pharm. Pharmacol.*, 1991, **43**, 735.
 6. L. Quatarra, M. Debaert, and R. Cavier, *Farmaco Ed. Sci.*, 1987, **42**, 449.
 7. N. Kornblum, P. Pink, and K. V. Yorka, *J. Am. Chem. Soc.*, 1961, **83**, 2779; N. Kornblum, R. E. Michel, and R. C. Kerber, *J. Am. Chem. Soc.*, 1966, **88**, 5660 and 5662.
 8. G. A. Russell and W. C. Danen, *J. Am. Chem. Soc.*, 1966, **88**, 5663.
 9. M. A. Nazareno and R. A. Rossi, *J. Org. Chem.*, 1996, **61**, 1645.
 10. M. P. Crozet, L. Giraud, J.-F. Sabuco, and P. Vanelle, *Tetrahedron Lett.*, 1992, **33**, 1063.
 11. W. J. Middleton, *J. Org. Chem.*, 1975, **40**, 574.
 12. P. Vanelle, *Thesis*, 1987, University of Aix-Marseille.
 13. W. R. Bowman, 'Photoinduced Electron Transfer: Photoinduced Nucleophilic Substitution at sp³-Carbon,' ed. by M. A. Fox, and M. Chanon, Elsevier, Amsterdam, 1988, Part C, Chap. 4.8, pp. 421-486.
 14. V. Béraud, P. Perfetti, C. Pfister, M. Kaafarani, P. Vanelle, and M. P. Crozet, *Tetrahedron*, 1998, **54**, 4923.
 15. M. Chanon and M. L. Tobe, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 1.
 16. R. Beugelmans and J. Chastanet, *Tetrahedron*, 1993, **49**, 7883.
 17. F. G. Bordwell and A. H. Clemens, *J. Org. Chem.*, 1981, **46**, 1035.
 18. R. K. Norris, S. D. Barker, and P. Neta, *J. Am. Chem. Soc.*, 1984, **106**, 3140.
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 20. R. C. Kerber, G. W. Urry, and N. Kornblum, *J. Am. Chem. Soc.*, 1965, **87**, 4520.

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