SYNTHESIS OF NEW 2-HIGHLY BRANCHED 5-NITRO-IMIDAZOLES BY BIS-$S_{RN}1$ METHODOLOGY

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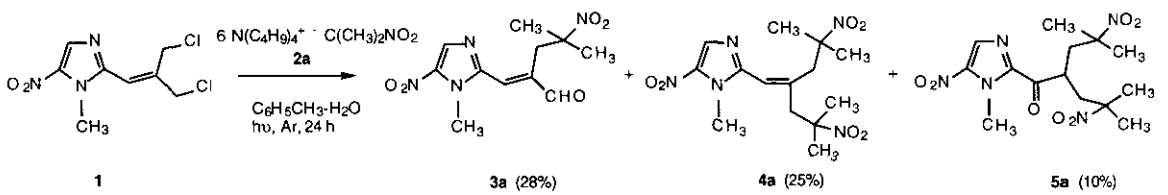
Abstract- A versatile bis-$S_{RN}1$ methodology allows straightforward access to 2-highly branched 5-nitroimidazoles by reacting 3-chloro-2-chloromethyl-1-(1-methyl-5-nitroimidazol-2-yl)prop-1-ene with various nitronate anions.

Since the initial proposal by Kornblum[1] and Russell[2] of the radical chain mechanism put forward to explain the *C*-alkylation of nitronate anions by *p*-nitrobenzyl chloride and its designation as $S_{RN}1$ by Bunnett,[3] there has been a booming development of the reaction both from synthetic and mechanistic points of view. The first bis-$S_{RN}1$ reaction has been recently disclosed in naphthoquinone series,[4] leading the bis-*C*-alkylation product in 80% yield. The unique heterocyclic example has been reported in imidazole series, but if the bis-*C*-alkylation product (**4a**) was obtained in 25% yield, the reaction of 3-chloro-2-chloromethyl-1-(1-methyl-5-nitroimidazol-2-yl)prop-1-ene (**1**) with 2-nitropropane anion (**2a**) gave also two other products proceeding by an initial $S_{RN}1$ mechanism followed by S_N2 or S_N2' and *Michael reactions* leading respectively to the aldehyde (**3a**) (28%) and the derivative (**5a**) (10%) as shown in Scheme 1.[5]

Scheme 1

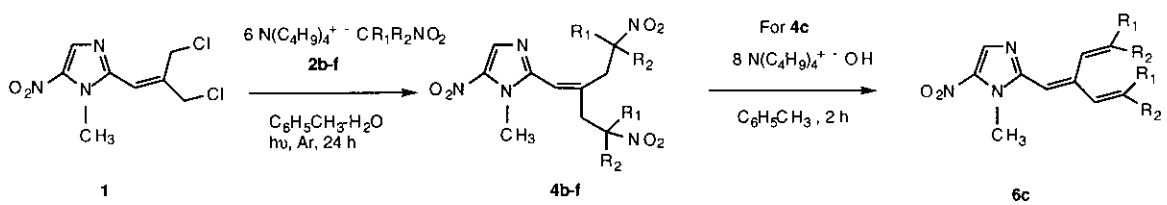


The nitroimidazoles, in particular metronidazole the most commonly used, are accepted as the drugs of choice for the chemotherapy of anaerobic bacteria and protozoal diseases and also for the radiosensitization of hypoxic tumors.[6] However, resistance to these compounds has been demonstrated in trichomonads and

in *Bacteroides fragilis*, both in natural populations and induced in the laboratory under drug pressure.[7] Moreover, certain nitroimidazoles have been found to be mutagenic and carcinogenic.[8] Thus, new principles for treatment of infections are therefore highly desirable.

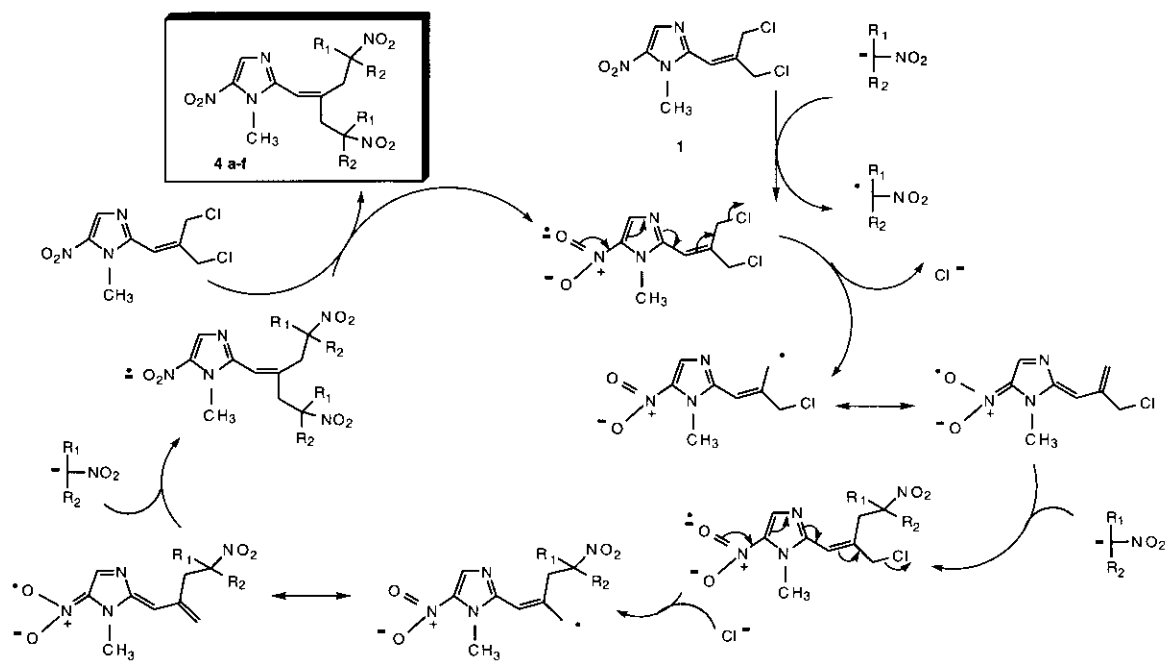
On the other hand, the nature of nucleophile is crucial to $S_{RN}1$ reactions, and therefore an understanding of the relationship between the nucleophile and the substrate in single electron transfer reaction is of use to increase the selectivity and the yield of the reaction.[9] In continuation of our program directed toward the preparation of new pharmacological compounds by $S_{RN}1$ reactions,[10] we have investigated the reactivity of **1** with various aliphatic, cyclic and heterocyclic nitronate anions. By using the same experimental conditions, phase-transfer conditions[11] with 40% tetrabutylammonium hydroxide in water and toluene and when the ratio of nitronate anion to bis-chloride was 6/1, only the bis-*C*-alkylation products (**4b-f**) were obtained in moderate to good yield (48 to 62%) as shown in Scheme 2 and indicated in table.

Scheme 2

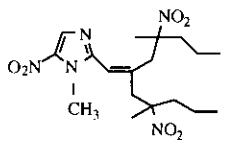
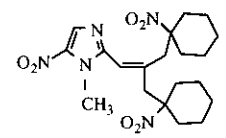
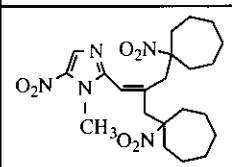
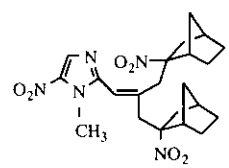
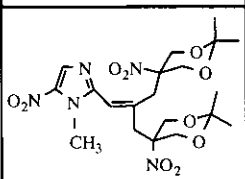


By comparison with **2a**, these results seem surprising but may be explained by possible intervention of secondary steric hindrances disfavoring the ionic competitive reactions of $S_{RN}1$, and the bis-$S_{RN}1$ as demonstrated in Scheme 3 was the predominant mechanism observed.

Scheme 3



Table

	Product of bis-*C*-alkylation **4**	Yield (%)	Formula Analysis data % Calcd; Found	mp (°C)	RMN ^{1}H (200MHz, $CDCl_3$)
b		48	$C_{18}H_{29}N_5O_6$ C, 52.54; 52.60 H, 7.10; 7.03 N, 17.02; 16.99	104	1:1 mixture of stereoisomers 0.94 (m, 3H); 0.97 (m, 3H); 1.17 (m, 2H); 1.42 (m, 2H); 1.49 (s, 3H); 1.51 (s, 3H); 1.77 (m, 2H); 2.05 (m, 2H); 2.18 or 3.10 (AX, J_{AX} = 14.1 Hz, 1H); 2.58 or 3.53 (AB, J_{AB} = 14.1 Hz, 2H); 3.87 or 3.88 (s, 3H); 2.92 or 4.10 (AX, J_{AX} = 14.1 Hz, 1H); 6.03 or 6.06 (s, 1H); 7.97 or 7.98 (s, 1H).
c		59	$C_{20}H_{29}N_5O_6$ C, 55.16; 55.20 H, 6.71; 6.80 N, 16.08; 16.10	180	1.26-1.33 (m, 4H); 1.56 (m, 12H); 2.40 (m, 4H); 2.51 (s, 2H); 3.41 (s, 2H); 3.88 (s, 3H); 5.97 (s, 1H); 7.99 (s, 1H).
d		51	$C_{22}H_{33}N_5O_6$ C, 57.01; 56.92 H, 7.18; 7.20 N, 15.11; 15.09	120	1.58 (m, 10H); 1.70-1.82 (m, 2H); 1.90-1.98 (m, 2H); 2.15 (dd, J = 15.3 and 8.1 Hz, 4H); 2.26-2.40 (m, 2H); 2.52 (s, 2H); 2.60 (dd, J = 15.6 and 8.2 Hz, 4H); 3.60 (s, 2H); 3.87 (s, 3H); 5.95 (s, 1H); 8.00 (s, 1H).
e		49	$C_{22}H_{29}N_5O_6$ C, 57.51; 57.60 H, 6.36; 6.40 N, 15.24; 15.30	172	1:1 mixture of stereoisomers 1.05-1.39 (m, 6H); 1.45-1.60 (m, 6H) 1.67 (m, 1H); 1.80 (m, 1H); 1.96 (m, 1H); 2.08 (m, 1H); 2.36 (m, 4H); 2.53 or 2.58 (AX, J_{AX} = 15.3 Hz, 1H); 3.05 or 3.08 (AX, J_{AX} = 15.3 Hz, 1H); 3.16 or 3.28 (AX, J_{AX} = 14.6 Hz, 1H); 3.85 or 3.86 (s, 3H); 4.18 or 4.24 (AX, J_{AX} = 14.6 Hz, 1H); 5.94 or 5.95 (s, 1H); 7.98 (s, 1H).
f		62	$C_{20}H_{29}N_5O_{10}$ C, 48.09; 48.10 H, 5.85; 5.79 N, 14.02; 13.95	104	1.41 (s, 6H); 1.46 (s, 6H); 4.00 (s, 3H); 4.15 (m, 2H); 4.28 (m, 2H); 4.35 (m, 2H); 4.42 (s, 2H); 4.47 (m, 2H); 5.00 (s, 2H); 6.52 (s, 1H); 8.06 (s, 1H);

By base-promoted nitrous acid elimination, new highly conjugated 5-nitroimidazoles of potential biological interest **6** may also be obtained: for example, **4c** in refluxing toluene with 8 equiv of 40% $N(C_4H_9)_4OH$ in water for 2 h, gave **6c** in 80% yield.

In conclusion, we have developed an original and easy access to new 2-highly branched 5-nitroimidazoles by using a bis-$S_{RN}1$ reaction and shown that crowded nitronates gave more selective reactions. The biological activities of these new 5-nitroimidazoles are under investigation.

ACKNOWLEDGEMENTS

The support of this work by the Centre National de la Recherche Scientifique is gratefully acknowledged. We thank Dr R. Faure for stimulating discussions about these spectroscopic data.

EXPERIMENTAL

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

The chloride (**1**) is obtained by chloration of 2-(1-methyl-5-nitro-1*H*-imidazol-2-ylmethylene)propane-1,3-diol[12] with thionyl chloride. The nitroalkanes (**2b-e**) are prepared from secondary amines by oxidation with *m*-CPBA in refluxing 1,2-dichloroethane for 3 h,[13] and 2,2-dimethyl-5-nitro-1,3-dioxane (**2f**) was obtained as previously described.[14]

General Procedure for $S_{RN}1$ reactions in Norris conditions

Under nitrogen atmosphere, an aqueous solution of 40% tetrabutylammonium hydroxide in water (7.9 mL, 12 mmol) reacted with nitroalkane or 2,2-dimethyl-5-nitro-1,3-dioxane (12 mmol) for 1 h. A solution of 3-chloro-2-chloromethyl-1-(1-methyl-5-nitroimidazol-2-yl)prop-1-ene (**1**) (0.50 g, 2 mmol) in 20 mL of toluene was added and the mixture was stirred for 24 h under nitrogen and irradiation with two 60 W fluorescent lamps. The organic layer was separated and the aqueous layer was extracted with three portions of toluene (20 mL). The combined organic layers were washed twice with 40 mL of water, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by chromatography on a silica gel column eluting with dichloromethane-ethyl acetate (95/5) and recrystallization from ethanol gave the bis-*C*-alkylation product (**4b-f**) as yellow solid.

2-(3-Cyclohexylidene-2-cyclohexylidenemethylpropenyl)-1-methyl-5-nitro-1*H*-imidazole (**6c**)

To a solution of 0.40 g (0.92 mmol) of 1-methyl-5-nitro-2-[3-(1-nitrocyclohexyl)-2-(1-nitrocyclohexylmethyl)propenyl]-1*H*-imidazole (**4c**) in 20 mL of toluene, an aqueous solution of 40% tetrabutylammonium hydroxide in water (4.8 mL, 7.3 mmol) was added. After 2 h refluxing, the organic layer was separated and the aqueous layer was extracted with toluene (3 x 20 mL). The combined organic layers were washed with water (3 x 50 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The crude solid was purified by chromatography on a silica gel column eluting with dichloromethane and recrystallization from hexane gave 0.25 g (80%) of the product as yellow needles, mp 91 °C, ^1H NMR ($CDCl_3$) δ 1.57-1.60 (m, 12H); 2.22-2.40 (m, 8H); 3.87 (s, 3H); 5.92 (br s, 2H); 6.33 (s, 1H); 8.08 (s, 1H). Anal. Calcd for $C_{20}H_{27}N_3O_2$: C, 70.35; H, 7.97; N, 12.31. Found: C, 70.40; H, 7.93; N, 12.30.

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Received, 18th September, 1997