CASCADE $S_{RN}1$ REACTIONS IN 5-NITROIMIDAZOLE SERIES

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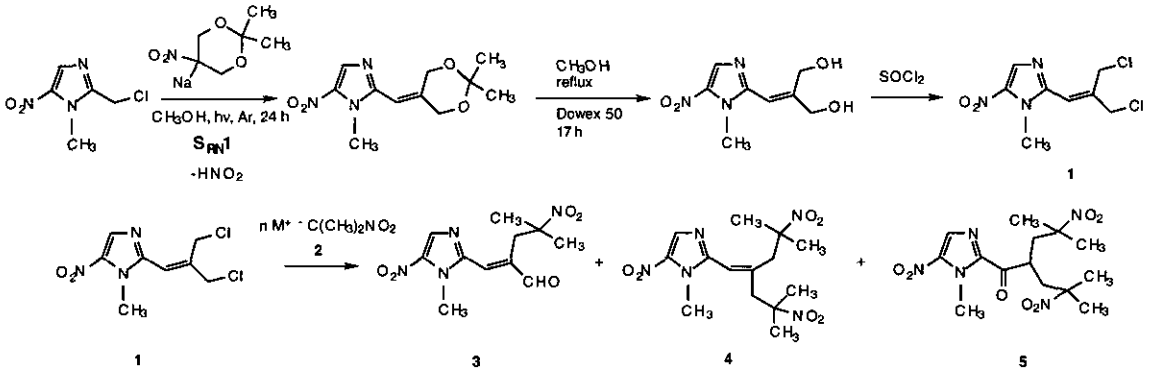
Abstract- The reaction of 3-chloro-2-chloromethyl-1-(1-methyl-5-nitro-imidazol-2-yl)prop-1-ene with 2-nitropropane anion which gives three products is shown to proceed by an initial $S_{RN}1$ mechanism followed by another $S_{RN}1$ leading to the bis-*C*-alkylation product or S_N2 or S_N2' and Michael reactions.

Since the introduction of the parent nitrogen mustard "HN2", new and more stable polyfunctional alkylating drugs have been developed in the search for more effective and less toxic agents.[1] Among these compounds, the bis(chloroethyl)amines as cyclophosphamide, melphalan or chlorambucil have the greatest utility by exerting cytotoxic effects *via* transfer of their alkyl group to various cellular constituents leading to cellular lethality. On the other hand, since the discovery in 1966 that carbon alkylation of ambident anions by *p*-nitrobenzyl chloride is an electron-transfer chain process termed $S_{RN}1$,[2] the extensions at sp^3 carbons attached to heterocyclic systems have been studied extensively.[3] In continuation of our program directed toward the study of bioreductive alkylating agents in $S_{RN}1$ reactions,[4] we have synthesized an original compound bearing two nucleofuges at allylic positions and far from the electron-withdrawing nitro group, 3-chloro-2-chloromethyl-1-(1-methyl-5-nitroimidazol-2-yl)prop-1-ene (**1**) and studied its reactivity with the 2-nitropropane anion in order to determine its electron-transfer alkylating properties.

The starting material (**1**) has been prepared following established procedures[5] in three steps from 2-chloromethyl-1-methyl-5-nitroimidazole and 5-nitro-1,3-dioxane salt by $S_{RN}1$ reaction followed by base-promoted nitrous acid elimination, acid-catalyzed cleavage of the resulting acetal and chloration. This bis-chloride (**1**) reacts with 2-nitropropane salt (**2**) under various conditions and gives three products[6] as shown in Scheme 1.

Scheme 1



Table

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

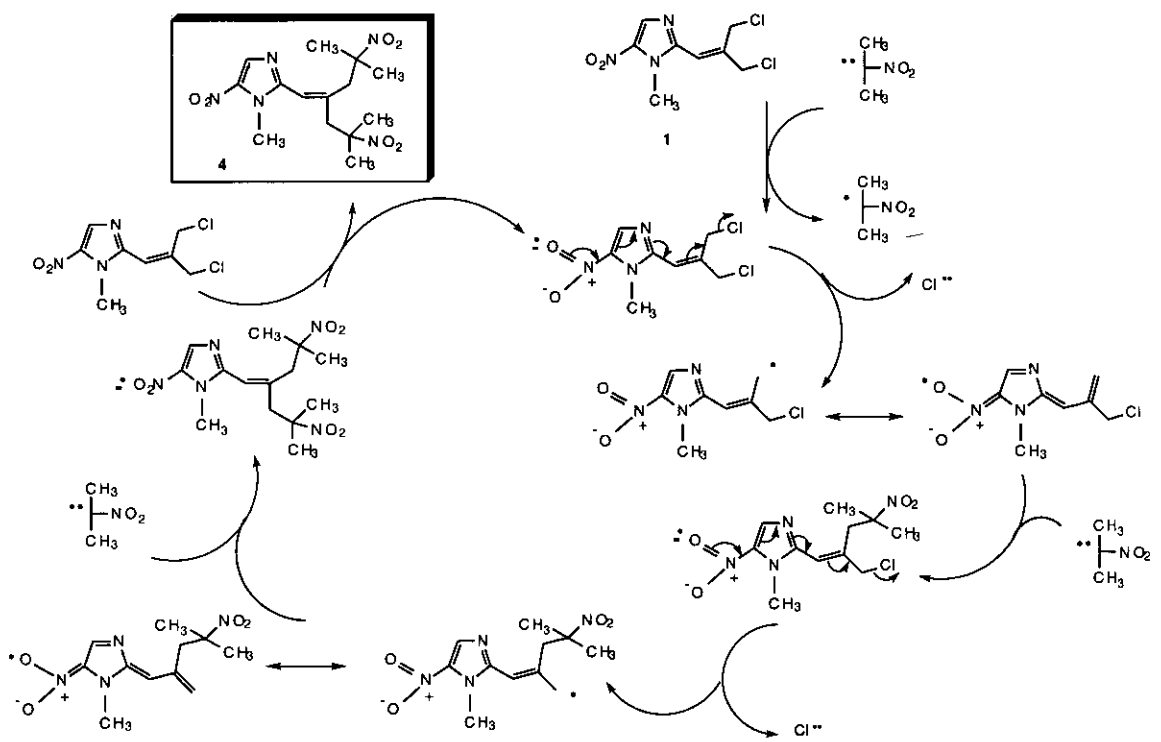
Entry	Mol. eq. of **2** (n)	M^+	Solvent	Time	Yield[b] **3**	**4**	**5**	**1**
1	5	Li	DMF	3 h	traces	traces	-	-
2	5	Li	DMSO	3 h	traces	traces	traces	-
3	5	$N(C_4H_9)_4$	CH_2Cl_2-H_2O[c]	12 h	5	traces	3	-
4	5	$N(C_4H_9)_4$	CH_2Cl_2-H_2O[d]	20 h	6	-	-	-
5	5	$N(C_4H_9)_4$	$C_6H_5CH_3$-H_2O[c]	24 h	56	9	15	-
6	5	Li	$C_6H_5CH_3$-H_2O[d]	125 h	15	traces	traces	30
7	5	Li	$C_6H_5CH_3$-H_2O[d,e]	2 h	12	4	6	-
8	3	$N(C_4H_9)_4$	$C_6H_5CH_3$-H_2O[c]	24 h	25	-	5	-
9	6	$N(C_4H_9)_4$	$C_6H_5CH_3$-H_2O[c]	24 h	28	25	10	-
10	8	$N(C_4H_9)_4$	$C_6H_5CH_3$-H_2O[c]	24 h	29	35	20	-
11	10	$N(C_4H_9)_4$	$C_6H_5CH_3$-H_2O[c]	24 h	18	32	10	-

[a]All reactions were performed by using one equivalent of **1** under nitrogen and irradiation with two 60W fluorescent lamps. [b]All yields were referred to chromatographically isolated pure products and relative to the electrophile. [c]Phase-transfer conditions with $N(C_4H_9)_4OH$ 40%. [d]Phase-transfer catalysis with $N(C_4H_9)_4$ Br. [e]The mixture was refluxed.

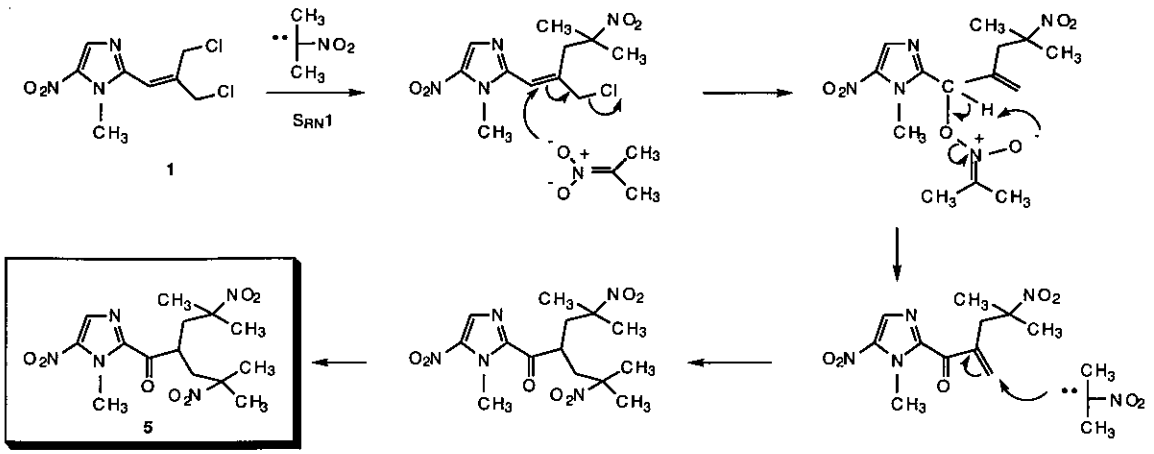
The above results show that the product distribution changes with the solvent and the ratio of the nucleophile to the substrate concentration. In DMF or DMSO, almost untraceable tarry materials are formed. Under phase-transfer conditions (tetrabutylammonium hydroxide 40% in water and toluene), when the ratio of nitronate anion to bis-chloride is 5/1, the original derivative (**3**) resulting of two classical and consecutive competing *C* and *O*-alkylation reactions on the same substrate is the predominant product while with 8 equivalents of 2-nitropropane anion, the bis-*C*-alkylation derivative (**4**) is the major product. For the derivative (**3**), only the *E* isomer was obtained as demonstrated by 2D-nmr proton chemical-shift spectroscopy at 400 MHz. With the same ratio of substrate to anion and under phase transfer catalysis using tetrabutylammonium bromide in water and toluene, the formation of **4** and **5** strongly decreases and starting bis-chloride (**1**) remains (30%) even after 125 h, but **1** completely reacts by heating at reflux during 2 h. The use of dichloromethane is detrimental for the yield of **4**. In these entries, another unexpected side-product (**5**) is obtained and its structure has been established from spectroscopic data: ^{1}H nmr (400 MHz), ^{13}C nmr and 2 D sequences.

To explain the formation of these products, we propose that the mono-*C*-alkylation derivative resulting of an initial $S_{RN}1$ mechanism is the key reactive intermediate which undergoes by another $S_{RN}1$ reaction leading to the bis-*C*-alkylation (**4**) product as shown in Scheme 2 or by an S_N2 mechanism to the derivative (**3**) or by S_N2' and Michael reactions to the product (**5**) as demonstrated in Scheme 3.

Scheme 2



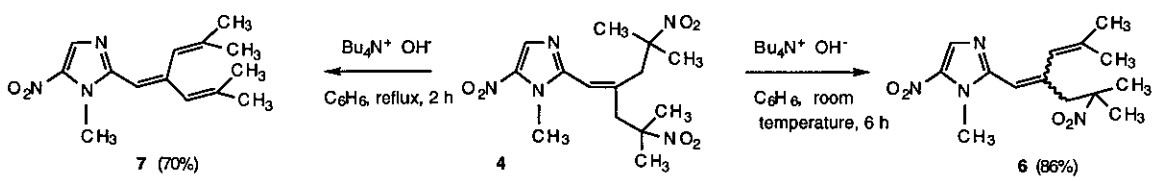
Scheme 3



The reaction of **1** with **2** was studied in presence of classical inhibitors[7] to confirm the nature of these cascade mechanisms. Complete inhibition was observed with one equivalent of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) showing the radical participation in the formation of the products. But, when bubbling dioxygen in the dark or by addition of *p*-dinitrobenzene, if the yields of **3** and **4** strongly decrease, the formation of derivative (**5**) which probably is an $S_{RN}1$ product in the first steps, is quite insensitive to the presence of these inhibitors. This discrepancy between the inhibition experiments would necessitate other studies to conclude in favour of an $S_{RN}1$ origin of **5**.

Base-promoted nitrous acid elimination from **4** gives the mono-unsaturated compound (**6**) by treating in benzene with 6 eq of NBu_4OH 40% in water at room temperature during 6h (86% yield) or the di-unsaturated compound (**7**) by heating at reflux during 2h (70% yield) as shown in Scheme 4.

Scheme 4



In conclusion, these results show that the bis-chloride (**1**) reacts with 2-nitropropane anion (**2**) to give 5-nitroimidazoles. It is the first example of a bis-$S_{RN}1$ reaction involving the imidazole system and a new way for the preparation of unknown 5-nitroimidazoles bearing multiple trisubstituted double bonds at the 2-position.

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6 All derivatives have been isolated as pure products and fully characterized: **1**, orange solid, mp 116 °C (ethanol), ^{1}H nmr ($CDCl_3$) δ 4.05 (s, 3H); 4.46 (d, J = 0.9 Hz, 2H); 5.03 (s, 2H); 6.55 (br s, 1H); 8.13 (s, 1H). **3**, white solid, mp 150 °C (isopropanol), ^{1}H nmr ($CDCl_3$) δ 1.58 (s, 6H); 3.74 (s, 2H); 4.11 (s, 3H); 7.16 (s, 1H); 8.10 (s, 1H); 9.65 (s, 1H). **4**, red solid, mp 104 °C (ethanol), ^{1}H nmr ($CDCl_3$) δ 1.64 (s, 6H); 1.66 (s, 6H); 2.66 (s, 2H); 3.63 (s, 2H); 3.91 (s, 3H); 6.11 (s, 1H); 8.01 (s, 1H). **5**, yellow solid, mp 96 °C (methanol), ^{1}nmr ($CDCl_3$) δ 1.56 (s, 6H); 1.62 (s, 6H); 2.03 (dd, J= 15.2 and 3.4 Hz, 2H); 2.61 (dd, J = 15.1 and 8.6 Hz, 2H); 4.26 (tt, J = 8.6 and 3.4 Hz, 1H); 4.30 (s, 3H); 8.01 (s, 1H). **6**, yellow solid, mp 112 °C (cyclohexane), ^{1}H nmr ($CDCl_3$) δ 1.61 (s, 6H); 1.82 (m, 3H); 1.90 (m, 3H); 3.60 (s, 2H); 3.95 (s, 3H); 5.58 (s, 1H); 6.12 (s, 1H); 8.05 (s, 1H). **7**, yellow solid, mp 86 °C (cyclohexane), ^{1}H nmr ($CDCl_3$) δ 1.71 (m, 3H), 1.87 (m, 9H); 3.90 (s, 3H); 5.92 (s, 1H); 5.97 (br s, 1H); 6.47 (br s, 1H); 8.09 (s, 1H).

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