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Long distance-$S_{RN}1$ in nitroimidazole series favored by temperature

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ABSTRACT

New reductive alkylating agents in 4- and 5-nitroimidazole series produce exclusively O-alkylation with nitronate anions under classical $S_{RN}1$ conditions at room temperature. Electron-transfer C-alkylation is observed under microwave irradiation or under conventional heating. Furthermore, X-ray spectroscopy shows that the dihedral angles between the phenyl and imidazole rings for the two series are different, which could greatly influence reactivity in 4- and 5-nitroimidazole series.

5-nitroimidazole scaffold is known to display major anti-infectious activities.[1] Several 5-nitroimidazole-containing active principles are commonly used in medicine. These chemotherapeutic agents inhibit the growth of anaerobic bacteria and of some anaerobic protozoa.[2] Nowadays, 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethanol (metronidazole) is the drug compound most frequently used clinically for the treatment of infections caused both by protozoa such as *Trichomonas vaginalis*, *Entamœba histolytica*, *Giardia intestinalis*, and by anaerobic bacteria.

However, 5-nitroimidazoles have been found to possess high mutagenic activity in prokaryotic micro-organisms.[3] Moreover, the emergence of metronidazole-resistant *T. vaginalis* is currently affecting therapeutic success.[4,5] These refractory cases are usually treated with higher doses of metronidazole, which leads to increased side effects.[5,6] A nitroimidazole offering good pharmacological activities against metronidazole-resistant *T. vaginalis* and *G. intestinalis*, with no mutagenicity, would be of great interest.[1b,e,7,8]

Unimolecular radical nucleophilic substitution ($S_{RN}1$) has been found to be an excellent synthetic pathway for many types of aromatic, heterocyclic, or aliphatic substrates with suitable leaving groups,[9] requiring substrates substituted with an electron-attracting group at the appropriate position.

Since Kornblum[10] and Russell[11] originally proposed the radical chain mechanism to explain the C-alkylation of nitronate anions by *p*-nitrobenzyl chloride, later designated as $S_{RN}1$ (unimolecular radical nucleophilic substitution) by Bunnett,[12] the extensions of this reaction at sp^3 carbon have been studied extensively.[13] These studies showed that ambident nitronate anion reacted by O-alkylation with benzylic halides. For example, benzyl chloride led to benzaldehyde only by O-alkylation with the 2-nitropropane anion from an S_N2 mechanism. In contrast, *p*-nitrobenzyle chloride reacted by C-alkylation with the 2-nitropropane anion, leading to the C-alkylated product.

Our previous study investigated a new $S_{RN}1$ reaction on (*E*)-2-[4-(chloromethyl)styryl]-1-methyl-5-nitro-1*H*-imidazole, involving a long distance (10 bonds) between the electron-withdrawing and leaving groups (LD-$S_{RN}1$). Unfortunately, when the chloride reacted with 2-nitropropane anion under various suitable conditions for the $S_{RN}1$ reaction (inert atmosphere, light), it only led to the aldehyde derivative through an S_N2 process (Scheme 1).[14]

These reactions are usually performed in DMSO at room temperature under inert atmosphere and photostimulation in order to initiate the $S_{RN}1$, but the influence of temperature on the competition between S_N2 and $S_{RN}1$ has never been evaluated.

Moreover, Geske showed in 1964 that the planarity of the nitrobenzyl group has an influence on this competition.[15] Indeed, *o*-nitrobenzyl chloride was more difficult to reduce than *p*-nitrobenzyl chloride, and provided 52% of *o*-nitrobenzaldehyde by O-alkylation. This has been established via the steric hindrance between the nitro group and the chloromethyl group on the phenyl ring in the *ortho* isomer, which decreased the coplanarity in the molecule. The system became less reducible by tending electronically to isolate the nitro group from the ring.

To further our work on $S_{RN}1$ (LD-$S_{RN}1$) reactivity and its limits in 5-nitroimidazole series and as part of a program aimed at the preparation of new and potentially safer nitroimidazoles, we

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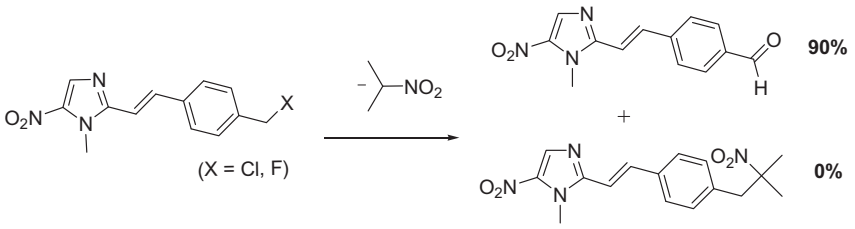
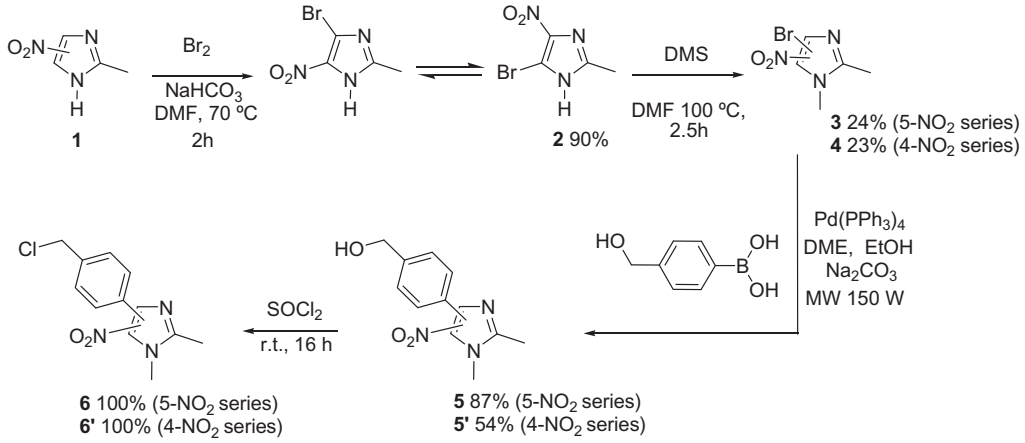


Scheme 1. (*E*)-2-[4-(Chloromethyl)styryl]-1-methyl-5-nitro-1*H*-imidazole reactivity with 2-nitropropane anion.

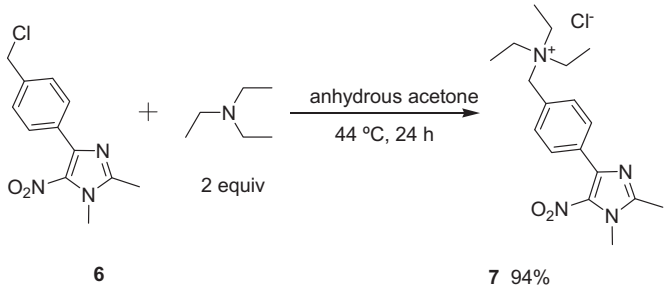


Scheme 2. Preparation of LD-$S_{RN}1$ precursors **6** and **6′**.

prepared 4(5)-[4-(chloromethyl)phenyl]-1,2-dimethyl-5(4)-nitro-1*H*-imidazoles and studied their reactivities with different nucleophiles, under $S_{RN}1$ experimental conditions (LD-$S_{RN}1$), in order to determine the reactivity of both isomers.

The starting material was obtained by the bromination of commercial 2-methyl-4(5)-nitro-1*H*-imidazole **1** with elemental bromine in DMF, methylation of **2** by dimethylsulfate to obtain **3**, which was then subjected to a Suzuki–Miyaura cross-coupling reaction to synthesize [4-(1,2-dimethyl-5-nitro-1*H*-imidazol-4-yl)phenyl]methanol **5**.[16] Chlorination of **5** with thionyl chloride provided 4-[4-(chloromethyl)phenyl]-1,2-dimethyl-5-nitro-1*H*-imidazole **6**,[17] which appeared to be a good candidate to investigate LD-$S_{RN}1$ (six bonds) (Scheme 2).

Furthermore, as alkylammonium chlorides are known to be poor leaving groups in S_N2 reactions,[9] we decided to synthesize and study the reactivity of *N*-[4-(1,2-dimethyl-5-nitro-1*H*-imidazol-4-yl)benzyl]-*N,N*-diethylethanaminium chloride **7**. *N,N,N*-Triethylethanaminium chloride derivative **7** was prepared in 94% yield from **6** with triethylamine (2 equiv) in anhydrous acetone at 44 °C for 24 h (Scheme 3).



Scheme 3. Preparation of **7**.

The first result in Table 1 shows that **6** reacts with the 2-nitropropane anion to give exclusively **10**[18] (entries 2, 6) resulting from an S_N2 O-alkylation with good yields under the usual $S_{RN}1$ conditions described by Kornblum (65% in DMSO–72% in DMF) at room temperature. Different $S_{RN}1$ reaction conditions were therefore examined, in order to study their influence on reactivity. Under conventional heating (oil-bath heating) in DMSO at 170 °C, a mixture of the expected C-alkylated products **8** (36%) and **9** (43%) resulting from the consecutive $S_{RN}1$ C-alkylation and base-promoted nitrous acid elimination were obtained (entry 8) without aldehyde **10**. In DMF at 140 °C, the reaction gave **8** (57%) and **10** (12%) (entry 4), but no trace of compound **9**. DMSO should solvate counterion in 2-nitropropane anion sodium salt better than DMF, inducing higher base strength in 2-nitropropane anion.[19]

With these encouraging results and on the basis of our previous studies,[20] we decided to evaluate the influence of microwave irradiation on the LD-$S_{RN}1$ reaction. The best microwave-assisted experimental conditions were defined, yielding in DMF a mixture of **8**[21] (60%), **10** (22%), and the appearance of **9**[21] (10%) (Table 1, entry 5). In DMSO, these conditions allowed the formation of **9** in 60% yields (entry 9).

Thus, no 'specific effect' (non-thermal effect)[22] from microwave irradiation was found and thermal effect alone appears sufficient to affect the main reaction from S_N2 to $S_{RN}1$.

As shown in entry 11 (Table 1), the use of the best experimental conditions cited above (Table 1, entry 5) with compound **7** gave a mixture of expected products **8** (44%) and **9** (32%). Moreover, no trace of aldehyde derivative was observed. These results suggest that both substrates **6** and **7** formed C-alkylated product by LD-$S_{RN}1$.

In order to confirm the single-electron transfer mechanism, inhibition reactions were performed (Table 2) by adding to the reaction mixture catalytic amounts (10 mol %) of cupric chloride ($CuCl_2$) or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), which