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# A CONVENIENT SYNTHESIS OF HIGHLY CONJUGATED 5-NITRO-IMIDAZOLES

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**Abstract** – A new series of highly conjugated 5-nitroimidazoles was prepared using electron transfer methodology in multi-steps synthesis from 2-chloromethyl-1-methyl-5-nitro-*1H*-imidazole.

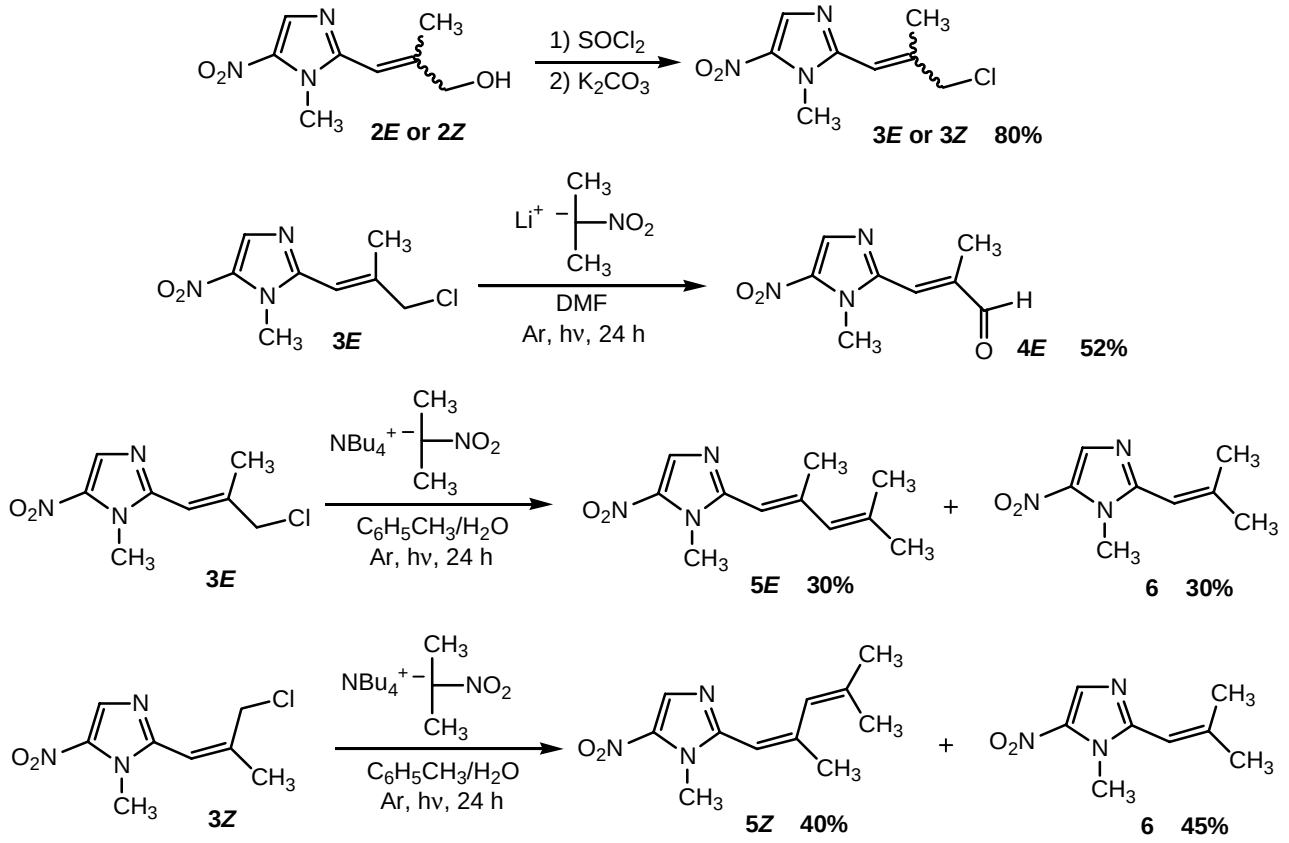
The introduction of nitroheterocyclic drugs in the late 1950s and the 1960s heralded a new era in the treatment of infections caused by gram-negative and gram-positive bacteria and a range of pathogenic protozoan parasites. The nitroimidazoles, in particular metronidazole the most commonly used, are accepted as the drugs of choice for the chemotherapy of anaerobic bacteria and protozoal diseases and also for the radiosensitization of hypoxic tumors.[1,2] However, resistance to these compounds has been demonstrated in trichomonads and *Bacteroides fragilis*, both in natural and under drug pressure *in vitro* induced populations.[3,4] Moreover, certain nitroimidazoles have been found to be mutagenic and carcinogenic.[5-7] On the other hand, our research program directed toward the synthesis of new potentially active nitroheterocyclic or quinonic compounds by electron transfer reactions ($S_{RN}1$, bis-$S_{RN}1$, Long Distance-$S_{RN}1$, $E_{RC}1$) permit us to prepare under mild conditions and in good yields highly substituted nitroheterocyclic or quinonic compounds.[8-11] In 5-nitroimidazole series, we have previously demonstrated that 2-chloromethyl-1-methyl-5-nitro-1*H*-imidazole (**1**) reacted with nitronate anions through electron transfer mechanisms.[12-16] Thus, a new class of 5-nitroimidazoles bearing a trisubtituted double bond at 2-position was obtained after nitrous acid elimination. The structure-activity relationship studies have revealed an increase of conjugation in the molecular structures of the most potent antimicrobial and antiparasitic compounds.[17,18] Recently, we have shown the efficacy of new conjugated 5-nitroimidazoles against metronidazole-susceptible and -resistant *Giarda*, *Trichomona*s, and *Entamoeba* spp.[19] In order to

increase the conjugated system, we have synthesized a series of new reductive alkylating agents using electron transfer methodology in multi-steps synthesis from 2-chloromethyl-1-methyl-5-nitro-*1H*-imidazole (**1**).

The starting material, 2-(3-chloro-2-methylpropenyl)-1-methyl-5-nitro-1*H*-imidazole (**3**) has been prepared as *E* and *Z* separable isomers in three steps from **1** and 2-nitro-1-propanol protected as tetrahydropyranyl ether by $S_{RN}1$ reaction, followed by base-promoted nitrous acid elimination, then acid-catalysed deprotection in methanol and chlorination.[18] The intermediate alcohol **2** was separated as *E* and *Z* isomers by column chromatography and the stereochemistry was established as previously.[18]

The reaction of **3*E*** in DMF, with 3 equivalents of 2-nitropropane anion after 24 h gave the aldehyde (**4*E***) in 52% yield resulting from an *O*-alkylation of nitronate anion ($S_N2$ mechanism). Moreover, in the same conditions the isomer **3*Z*** led to untractable tarry matters. However, the reaction of **3*E*** or **3*Z*** with 3 equivalents of 2-nitropropane anion in phase-transfer conditions (1.6 M tetrabutylammonium hydroxide in water and toluene) led to the substitution product (**5*E***) or (**5*Z***) and the reduction product (**6**) was also isolated, as shown in Scheme 1.

**Scheme 1**

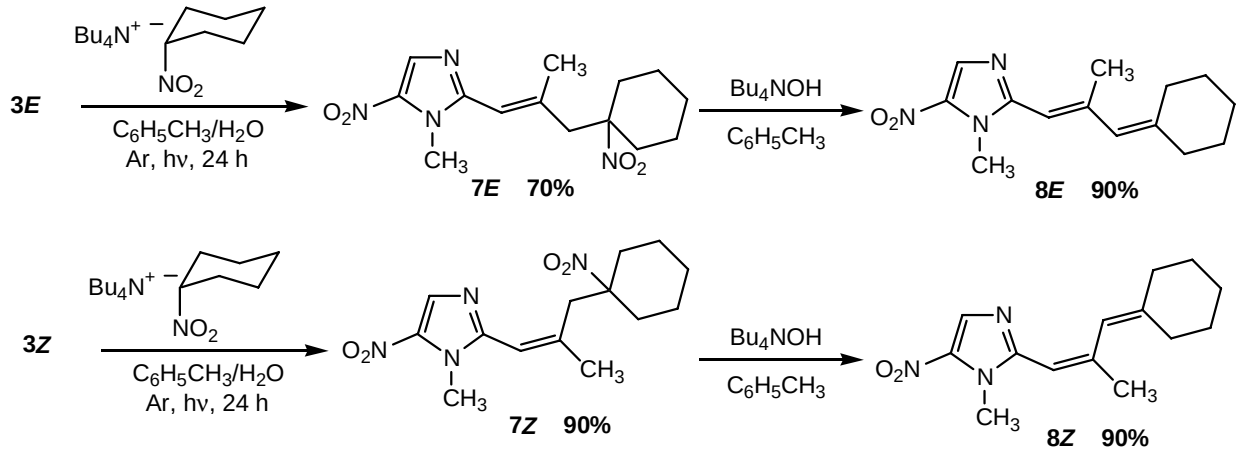



The ethylenic derivatives (**5*E***) and (**5*Z***) were obtained by a base promoted nitrous acid elimination of the corresponding *C*-alkylation product which were formed according to an $S_{RN}1$ mechanism, whereas the by-product (**6**), isolated in the two reactions, was formed by a single electron transfer (SET)

reduction.[20,21] As shown in the bis-$S_{RN}1$ reactivity of 3-chloro-2-chloromethyl-1-(1-methyl-5-nitro-1*H*-imidazol-2-yl)prop-1-ene where the two chlorine atoms were chemically different,[13,14] the two isomers of chloride (**3**) react differently. This difference may be explain, for the **3*Z*** isomer, by a nucleophilic assistance of nitrogen atom at the position 3 of imidazole which favors the radical anion decomposition and stabilizes the allylic radical formed leading to a better $S_{RN}1$ reactivity.

Finally, the extension of this reaction with other nitronate anions, as nitrocyclohexane anion led to the *C*-alkylation product (**7*E***) or (**7*Z***) in a yield which is better with *Z* isomer (90%) than the *E* isomer (70%) as observed with 2-nitropropane anion. In this example, the nitrous acid elimination was not observed, this result should be related to the steric hindrance of nitrocyclohexane anion. In order to increase the conjugated system, treatment of these derivatives with a solution of tetrabutylammonium hydroxide (1.6 M in water) in toluene furnished the ethylenic compound (**8*E***) or (**8*Z***) in 90% yield (Scheme 2).

**Scheme 2**




In conclusion, we have synthesized a series of new highly conjugated 5-nitroimidazole derivatives by a multi-steps synthesis including electron transfer processes. The pharmacological evaluation of these new 5-nitroimidazoles is in progress.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## EXPERIMENTAL

Melting points were determined on Büchi B-540 and are uncorrected. Elemental analyses were performed by the Centre de Microanalyses of the University of Aix-Marseille 3. $^1$H and $^{13}$C NMR spectra were determined on Bruker ARX 200 spectrometer. The $^1$H chemical shifts are reported as parts per million

downfield from tetramethylsilane ($Me_4Si$). Solvents were dried by conventional methods. The following adsorbent was used for column chromatography : silica gel 60 (Merck, 230-400 mesh). TLC was performed with silica gel Merck 60F-254 (0.25 mm layer thickness).

2-Chloromethyl-1-methyl-5-nitro-1*H*-imidazole (**1**), 2-methyl-3-(1-methyl-5-nitro-1*H*-imidazol-2-yl)-prop-2-en-1-ol (**2**) and 1-methyl-2-(2-methylpropenyl)-5-nitro-1*H*-imidazole (**6**) were previously described.[18]

**2-(3-Chloro-2-methylpropenyl)-1-methyl-5-nitro-1*H*-imidazole (3)**

Thionyl chloride (5.27 mL, 72.25 mmol) was added dropwise to a solution of 2-methyl-3-(1-methyl-5-nitro-1*H*-imidazol-2-yl)prop-2-en-1-ol (**2*E***) or (**2*Z***) (2.37 g, 12.04 mmol) in dichloromethane (50 mL) in a round-bottomed flask equipped with a reflux condenser mounted by a calcium chloride drying tube. After stirring for 24 h, the reaction mixture was evaporated under reduced pressure. The residue was poured into water, basified with saturated sodium bicarbonate solution. After extraction with dichloromethane (3 x 10 mL), the organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure. Purification by recrystallization from appropriate solvent gave 2.08 g (80%) of 2-(3-chloro-2-methylpropenyl)-1-methyl-5-nitro-1*H*-imidazole (**3*E***) or 2.08 g (80%) of **3*Z***.

**2-(3-Chloro-2-methylpropenyl)-1-methyl-5-nitro-1*H*-imidazole (3*E*)**

Orange needles, mp 84 °C (ethanol), $^1$H NMR ($CDCl_3$) δ 2.29 (s, 3H); 3.95 (s, 3H); 4.19 (d, J = 0.9 Hz, 2H); 6.37 (s, 1H); 8.07 (s, 1H). $^{13}$C NMR ($CDCl_3$) δ 17.34; 33.06; 50.37; 112.65; 133.17; 138.54; 146.83; 148.32. Anal. Calcd for $C_8H_{10}N_3O_2Cl$ : C, 44.56; H, 4.67; N, 19.49; Cl, 16.44. Found : C, 44.60; H, 4.66; N, 19.35; Cl, 16.50.

**2-(3-Chloro-2-methylpropenyl)-1-methyl-5-nitro-1*H*-imidazole (3*Z*)**

Orange needles, mp 74 °C (isopropyl alcohol), $^1$H NMR ($CDCl_3$) δ 2.16 (s, 3H); 3.95 (s, 3H); 4.76 (s, 2H); 6.16 (s, 1H); 8.06 (s, 1H). Anal. Calcd for $C_8H_{10}N_3O_2Cl$ : C, 44.56; H, 4.67; N, 19.49; Cl, 16.44. Found : C, 44.53; H, 4.70; N, 19.20; Cl, 16.50.

**$S_{RN}$1 reaction of chloride (3*E*) with 2-nitropropane salt in DMF**

2-Nitropropane lithium salt (0.57 g, 6 mmol) in dry DMF (4 mL) was added to a solution of 2-(3-chloro-2-methylpropenyl)-1-methyl-5-nitro-1*H*-imidazole (**3*E***) (0.43 g, 2 mmol) in dry DMF (10 mL). The reaction was allowed to proceed for 24 h at rt under nitrogen and in the presence of light (300 W fluorescent lamp). After stirring, the reaction mixture was evaporated under reduced pressure. The residue was dissolved in dichloromethane (40 mL), washed with water (2 x 30 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Purification by chromatography on silica gel eluting with dichloromethane and recrystallization from isopropyl alcohol gave 0.21 g (52%) of 2-methyl-3-(1-methyl-5-nitro-1*H*-imidazol-2-yl)propenal (**4*E***).

**2-Methyl-3-(1-methyl-5-nitro-1*H*-imidazol-2-yl)propenal (4*E*)**

Orange needles, mp 78 °C (isopropyl alcohol), $^1$H NMR ($CDCl_3$) δ 2.35 (s, 3H); 4.10 (s, 3H); 6.99 (s, 1H); 8.10 (s, 1H); 9.68 (s, 1H). Anal. Calcd for $C_8H_9N_3O_3$ : C, 49.23; H, 4.65; N, 21.53. Found : C, 49.25; H, 4.70; N, 21.44.

**$S_{RN}$1 reaction of chloride (3*E*) or (3*Z*) and 2-nitropropane in phase-transfer conditions**

Under nitrogen atmosphere, a solution of tetrabutylammonium hydroxide (1.6 M/water, 4.63 mL, 6.95 mmol) was treated with 2-nitropropane (0.62 g, 6.95 mmol) for 1 h. A solution of chloride (**3*E***) or (**3*Z***) (0.5 g, 2.32 mmol) in toluene (10 mL) was added and the mixture was irradiated with a 300 W sun lamp for 12 h. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed twice with water (30 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Purification by chromatography on silica gel eluting with dichloromethane gave 0.15 g (30%) of 2-(2,4-dimethylpenta-1,3-dienyl)-1-methyl-5-nitro-1*H*-imidazole (**5*E***) and 0.12 g (30%) of 1-methyl-2-(2-methylpropenyl)-5-nitro-1*H*-imidazole (**6**) or 0.20 g (40%) of isomer (**5*Z***) and 0.20 g (45%) of **6**.

**2-(2,4-Dimethylpenta-1,3-dienyl)-1-methyl-5-nitro-1*H*-imidazole (5*E*)**

Yellow solid, mp 51 °C (hexane), $^1$H NMR ($CDCl_3$) δ 1.85 (s, 3H); 1.89 (s, 3H); 2.26 (s, 3H); 3.90 (s, 3H); 5.85 (s, 1H); 6.98 (s, 1H); 8.07 (s, 1H). Anal. Calcd for $C_{11}H_{15}N_3O_2$ : C, 59.71; H, 6.83; N, 18.99. Found : C, 59.66; H, 6.80; N, 19.03.

**2-(2,4-Dimethylpenta-1,3-dienyl)-1-methyl-5-nitro-1*H*-imidazole (5*Z*)**

Yellow solid, mp 43 °C (hexane), $^1$H NMR ($CDCl_3$) δ 1.90 (s, 3H); 1.91 (s, 3H); 2.27 (s, 3H); 3.91 (s, 3H); 5.86 (s, 1H); 6.00 (s, 1H); 8.08 (s, 1H). Anal. Calcd for $C_{11}H_{15}N_3O_2$ : C, 59.71; H, 6.83; N, 18.99. Found : C, 59.72; H, 6.85; N, 19.02.

**$S_{RN}$1 reaction of chloride (3*E*) or (3*Z*) and nitrocyclohexane-** As with 2-nitropropane, the same phase-transfer conditions were used for the reaction of **3*E*** or **3*Z*** and nitrocyclohexane. These reactions gave 0.50 g (70%) of the 1-methyl-2-[2-methyl-3-(1-nitrocyclohexyl)propenyl]-5-nitro-1*H*-imidazole (**7*E***) or 0.65 g (90%) of isomer (**7*Z***).

**1-Methyl-2-[2-methyl-3-(1-nitrocyclohexyl)propenyl]-5-nitro-1*H*-imidazole (7*E*)**

Yellow solid, mp 112 °C (ethanol), $^1$H NMR ($CDCl_3$) δ 1.25-1.60 (m, 8H); 2.25 (s, 3H); 2.40 (m, 2H); 3.63 (s, 2H); 3.84 (s, 3H); 5.85 (s, 1H); 7.88 (s, 1H). Anal. Calcd for $C_{14}H_{20}N_4O_4$ : C, 54.54; H, 6.54; N, 18.17. Found : C, 54.52; H, 6.60; N, 18.19.

**1-Methyl-2-[2-methyl-3-(1-nitrocyclohexyl)propenyl]-5-nitro-1*H*-imidazole (7*Z*)**

Yellow solid, mp 110 °C (ethanol), $^1$H NMR ($CDCl_3$) δ 1.29-1.70 (m, 8H); 2.10 (s, 3H); 2.48 (m, 2H); 2.71 (s, 2H); 3.83 (s, 3H); 5.84 (s, 1H); 7.98 (s, 1H). $^{13}$C NMR ($CDCl_3$) δ 21.21; 22.31; 24.54; 33.07; 34.55; 51.16; 92.13; 114.60; 133.09; 138.41; 145.91; 148.61. Anal. Calcd for $C_{14}H_{20}N_4O_4$ : C, 54.54; H, 6.54; N, 18.17. Found : C, 54.50; H, 6.63; N, 18.16.

**Nitrous acid elimination on 7*E* or 7*Z***

A solution of 1-methyl-2-[2-methyl-3-(1-nitrocyclohexyl)propenyl]-5-nitro-1*H*-imidazole (**7*E***) or (**7*Z***) (0.14 g, 0.46 mmol) in toluene (10 mL) was refluxed with a solution of tetrabutylammonium hydroxide (1.6 M/water, 2.45 mL, 3.68 mmol) for 2 h. The organic layer was separated and the aqueous layer was extracted with toluene (3 x 10 mL). The combined organic layers were washed twice with water (30 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Purification by chromatography on silica gel eluting with dichloromethane gave 0.11 g (90%) of 2-(3-cyclohexylidene-2-methylpropenyl)-1-methyl-5-nitro-1*H*-imidazole (**8*E***) or (**8*Z***).

**2-(3-Cyclohexylidene-2-methylpropenyl)-1-methyl-5-nitro-1*H*-imidazole (8*E*)**

Yellow solid, mp 59 °C (hexane), $^1$H NMR ($CDCl_3$) δ 1.43 (m, 6H); 2.15 (m, 2H); 2.28 (s, 3H); 2.39 (m, 2H); 3.92 (s, 3H); 5.84 (s, 1H); 6.54 (s, 1H); 8.07 (s, 1H). Anal. Calcd for $C_{14}H_{19}N_3O_2$ : C, 64.35; H, 7.33; N, 16.08. Found : C, 64.45; H, 7.30; N, 16.12.

**2-(3-Cyclohexylidene-2-methylpropenyl)-1-methyl-5-nitro-1*H*-imidazole (8*Z*)**

Yellow solid, mp 56 °C (hexane), $^1$H NMR ($CDCl_3$) δ 1.56 (m, 6H); 2.20 (m, 2H); 2.26 (s, 3H); 2.42 (m, 2H); 3.91 (s, 3H); 5.80 (s, 1H); 5.99 (s, 1H); 8.09 (s, 1H). Anal. Calcd for $C_{14}H_{19}N_3O_2$ : C, 64.35; H, 7.33; N, 16.08. Found : C, 64.40; H, 7.35; N, 16.10.

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