Nucleophilic Substitution Studies on Nitroimidazoles, and Applications to the Synthesis of Biologically Active Compounds

Gérard Chauvière*, Cécile Viodé and Jacques Périé

Groupe de Chimie Organique Biologique, ESA 5068 du CNRS, Bat 2R1,
Université P. Sabatier, 118 route de Narbonne, 31062 Toulouse, France
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The rationalization of the synthesis of substituted analogs of megazol, a biologically active 5-nitroimidazole at position 4 of the imidazole ring, had led to the study of intermediate steps. The methylation by diazomethane of 2,4-(5)dihalogeno-5-(4)nitroimidazole is regioselective leading to 2,4-dihalogeno-1-methyl-5-nitroimidazole **2**. On this compound **2**, hard nucleophiles such as cyanide, methoxide or hydride anions react only with the halogen at the 2 position; whereas soft nucleophiles such as amine, thiol or trifluoromethyl anion from an organocopper species react only with the halogen at postion 4 in the intermediate **3b** or compound **4b**.

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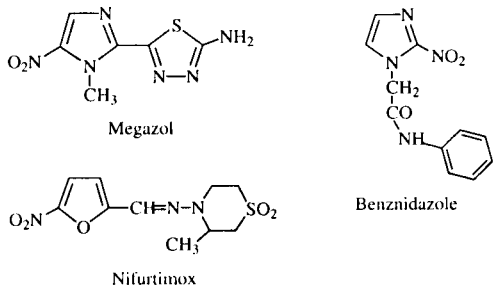
Introduction.

In the last few decades, nitroimidazoles have been the source of many investigations due to their properties as antibiotics, radiosensitizers and anti-protozoans [1,2,3]. We have studied specifically a 5-nitroimidazole named Megazol (Scheme 1), initially synthesized at American Cyanamid [4] and which is the subject of renewed interest after Brazilian

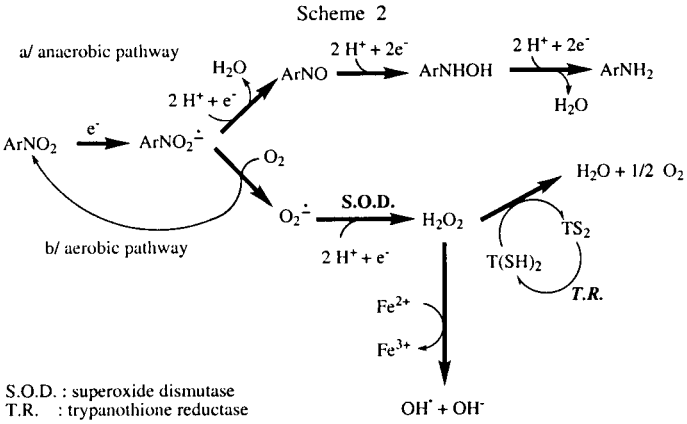
Scheme 1



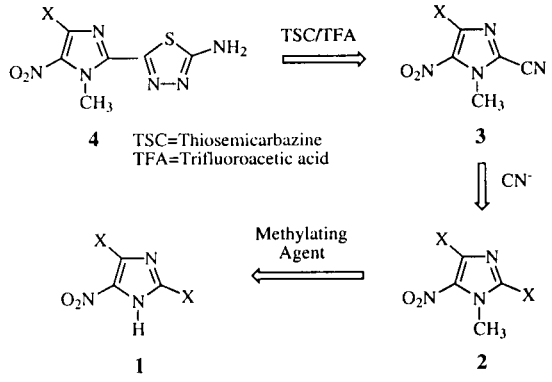
research workers demonstrated its high efficiency on *Trypanosoma cruzi* [5], the parasite responsible for Chagas disease in South America. These results are of great significance since this compound represents a promising alternative once Nifurtimox has been withdrawn from the market due to the resistance developed by many strains to this drug and similar problems associated with Benznidazole. Futhermore, we observed that Megazol efficiency could be extended to *Trypanosoma brucei*, the pathogenic agent of African trypanosomiasis [6,7].

After showing that Megazol in the trypanosoma undergoes a bioreduction leading first to a radical anion which then gives oxygen activated species [8] (Scheme 2), it was considered worthwhile to synthesize analogs where substituents may change the stability of the first radical anion, and therefore improve its redox-cycle properties. This was done by introducing either electron-donating or electron-withdrawing groups at position 4. This led to reconsidering the whole strategy for the synthesis of Megazol analogs, following the retrosynthetic process described in Scheme 3. The route is based on nucleophilic halogen substitution in imidazoles activated

Scheme 2



Scheme 3



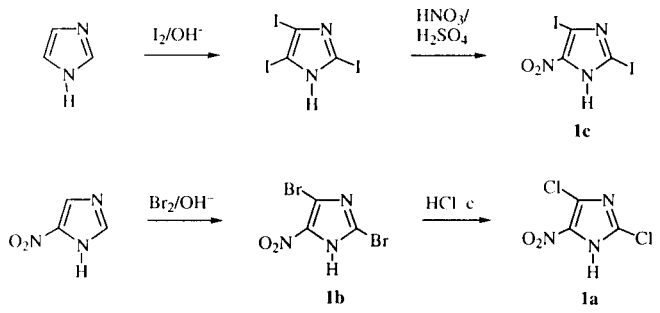
by the nitro group starting from 2,4-(5)-dihalo-5-(4)-nitroimidazoles obtained as indicated in Scheme 4. This work is therefore devoted to the study of the reactivity of nucleophiles on the intermediates obtained in different steps of the synthesis.

Results and Discussion.

1 - Synthesis of 2,4-(5)-Dihalo-5-(4)-nitroimidazoles.

A first route previously described in the literature [9] involves nitroimidazole as the starting material which allows formation of **1b** by bromination under basic conditions. Compound **1a** was obtained from **1b** by reaction of hydrochloric acid on **1b** (Scheme 4).

Scheme 4



Iodination of 5-(4)-nitroimidazole was unsuccessful, thus compound **1c** was obtained by ipso nitration of the triiodoimidazole under standard conditions [10,11]. The nitration at position 2 was not observed using these conditions, due to poor stabilization of the positive charge between the two vicinal nitrogen atoms. The bromine atom in tribromo imidazole did not undergo ipso nitration under these conditions.

2 - Methylation of 2,4-(5)-dihalogeno-5-(4)-nitroimidazoles

Regioselectivity for the isomer bearing the nitro group at position 5 was sought by using different experimental conditions, reagents, solvents and temperature. The tautomeric equilibrium of compound **1** is similar to that of the starting material nitroimidazole which is well documented [12] and the 4-nitro derivative is more stable in solution. The same study indicates that for the corresponding methylated products, the 1-methyl-4-nitro is more stable in solution than the 1-methyl-5-nitro derivative, by 2.7 kcal. Results corresponding to the reaction in Scheme 5 are given in Table 1.

These can be rationalized as follows:

With dimethyl sulfate as a reagent, mixtures are obtained whatever the solvent temperature or medium; it can be noted however that the less stable 5-nitro compound is the major isomer in the more polar solvents, acetonitrile and dimethylformamide, or put another way, in conditions where the transition states relating to the 4 and 5-nitro compounds are lowered. Using a basic medium likely to induce equilibrating conditions (potassium carbonate in acetone), the 4-nitro isomer becomes prevalent even at lower temperatures. The same is true using methyliodide, although the yield is improved. The best results are obtained with diazomethane, which allows a quantitative reaction at room temperature and leads to a ratio 95:5 in favour of the desired product. Identical results were obtained with **1a**, **1b** and **1c**, showing that the 5-nitro-1-methyl derivative is the kinetic product, and the 1-methyl-4-nitro, the more stable thermodynamic product [13]. Under kinetic conditions (low temperature, neutral medium), the early transition state (highly reactive reagent) leads to compound **2** in an almost quantitative yield.

Scheme 5

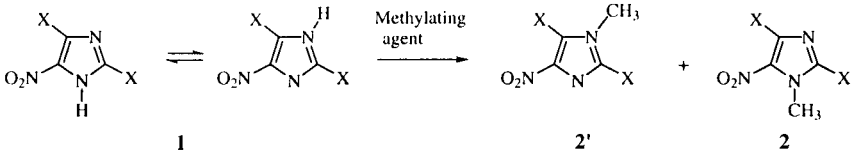


Table 1

Methylation reactions of 2,4(5)-dihalogeno-5-(4)-nitro imidazoles **1a,b,c**

Compound	Reagent	t°C	solvent	time (h)	yield [a] (%)	ratio [b] **2/2'**
1a X = Cl **1b** X = Br **1c** X = I						
1b	Me_2SO_4	100	Dioxane	18	30	50/50
1b	"	100	+NaOH	2	90	25/75
1b	"	100	DMF	2	75	75/25
1b	"	75	DMSO	18	40	50/50
1b	"	70	CH_3CN	18	40	75/25
1b	"	40	Acetone (K_2CO_3)	18	30	40/60
1b	CH_3I	110	DMF (K_2CO_3)	4	90	40/60
1b	CH_2N_2	20	THF	1	100	95/5
1a	"	"	"	"	"	"
1c	"	"	"	"	"	"

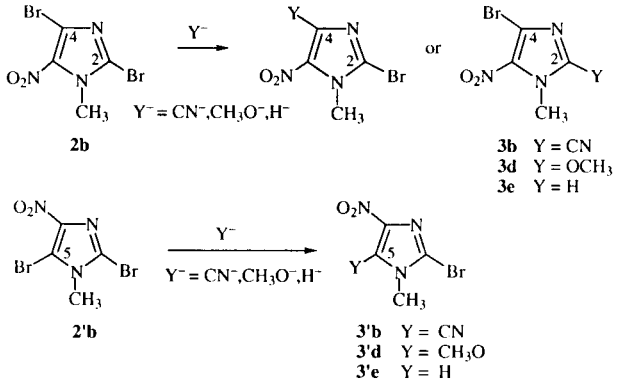
[a] Calculated from the relative intensities of N-CH_3 signal at 3.73 ppm for **2'a** and 4 ppm for **2**. [b] Yield of the mixture of **2** and **2'** isolated by column chromatography.

3 - Nucleophilic substitutions on regio-isomers **2** and **2'**.

a) by cyanide ion:

As the next target was compound **3b** with a nitrile group at position 2, the reactions corresponding to Scheme 6 were investigated. In this way, reaction of compound **2b** with potassium cyanide in dimethyl sulfoxide and in the presence of

Scheme 6



18-crown-6 ether at 80°, allows the formation of a single isomer (single N methyl signal in nmr δ ^{1}H 4.18 ppm ^{13}C 37.3 ppm) in a 80% yield. The substitution appears more likely at position 2, because it results from a reaction intermediate with more extended conjugation, than for substitution at position 4. Substitution at position 2 was verified by X-ray crystallography, the only spectroscopic method capable of differentiating between substitution at position 2 and 4 [14] (Figure 1).

The other regioisomer **2'b** did not react in identical conditions: after 24 hours, only 10% of substitution at position 5 occurred. This result can be accounted for by the fact that the corresponding intermediate is poorly stabilized. Reaction at position 2 did not occur either.

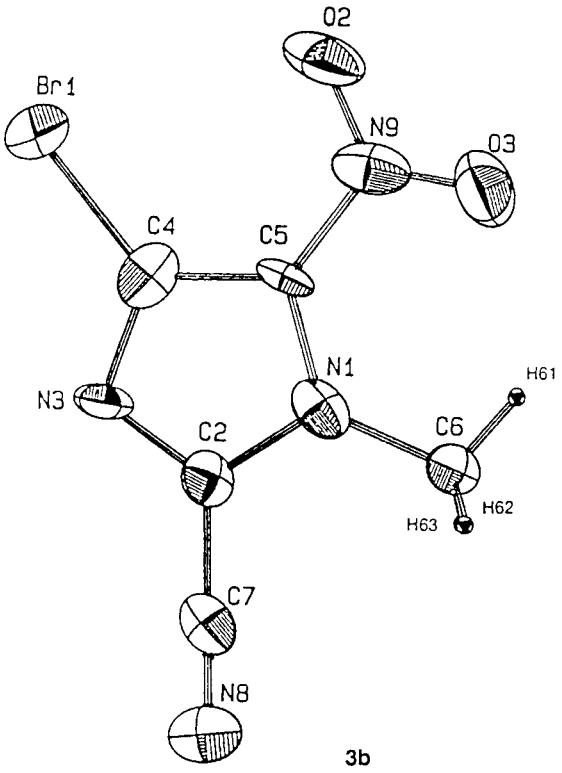
b) by methoxide ion:

Results obtained with cyanide ion were confirmed by reaction of **2b** and **2b'** with sodium methoxide in methanol. After refluxing for for three hours, compound **2b**, led quantitatively to a single substituted product, the structure of which was also determined by X-ray crystallography [14] (Figure 1).

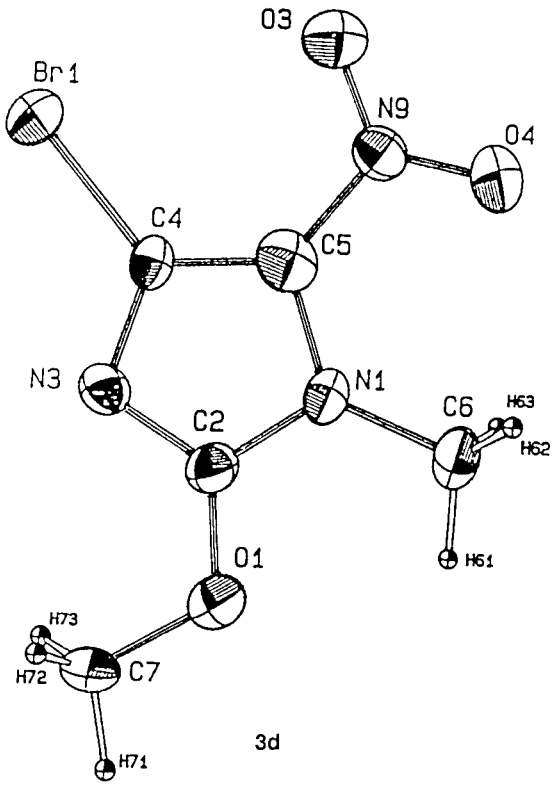
The other isomer **2'b** was found to be much less reactive, since after ten hours refluxing, only 40% of substitution at position 5 occurred. This structure was confirmed by comparison of the corresponding ^{1}H and ^{13}C nmr spectra to those of 1-methyl-5 methoxy-4 nitro imidazole previously described [15].

c) by hydride ion:

The reaction of sodium borohydride in dimethyl sulfoxide showed the same regiospecificity, where isomer **2b**, yielded compound **3e** by substitution at C2 exculsively; under the



3b



3d

same conditions isomer **2'** reacted only at the 5 position, leading to **3'e**.

The structure of **3e** has been previously described[15], and that of **3'e** is determined by reference to **2'b** by ^1H and ^{13}C nmr.

4 - Nucleophilic substitution on the 4-bromo-2cyano-1-methyl-5nitro imidazole **3b**.

a) Reaction of: Trifluoromethyl copper generated *in situ*.

This organometallic compound was prepared by redistribution of trifluoromethyl cadmium, from dibromodifluoromethene in dimethylformamide according to Burton [17]. Reaction on **3b** in hexamethylphophoramide at 70°, leads to **5**, with the trifluoromethyl group attached at position 4, in 60% yield (Scheme 7). The structure of compound **5** was confirmed by comparing nmr, ir and mass spectral data of **5** with that of compound **3**.

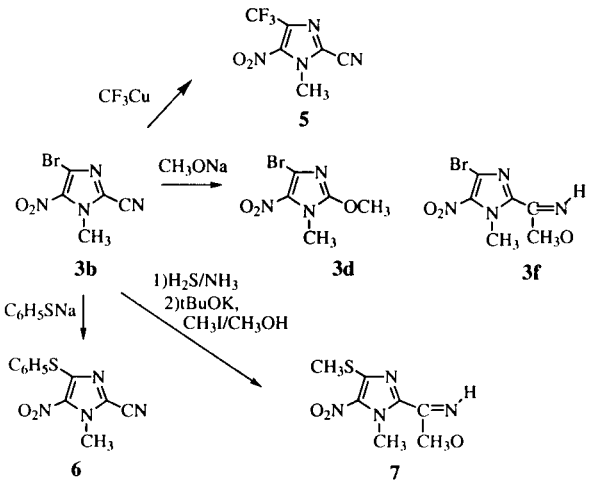
b) Reaction of: Sodium methoxide.

At room temperature, this reagent leads essentially to imidate **3f** resulting from addition to the nitrile attached at position 2. A second product was obtained in a lesser extent, resulting from the substitution of the cyano group by methoxide ion. No reaction occured at position 4.

c) Reaction of: Thiols.

Reaction with hydrogen sulfide in ammonia on compound **3b** in tetrahydrofuran gave a red solid compound, probably an ammonium sulfide, since further reaction in methanol with potassium *tert*-butoxide and methyl iodide led to product **7** bearing the methylthio group at position 4, as deduced from nmr spectroscopy. With sodium phenyl sulfide, compound **6** was obtained in a 75% yield, once again, with substitution at position 4 (Scheme 7).

Scheme 7



Based on the results in sections 3 and 4, substitutions at either position 2 or 4 can be rationalized in terms of hard or soft character of the different nucleophiles. For example, carbon 4 is much softer than carbon 2, due to the strong polarizability of the double bond C_4-C_5 imposed by the nitro group. Hence, the soft nucleophiles trifluoromethyl copper, methyl sulfide and phenyl sulfide, react at this position in high yield. Conversely, hard nucleophiles such as methoxide or hydride ions react at position 2: sodium methoxide gives mainly an imidate by addition on the nitrile group and no substitution at position 4. The same is true of compound **2b** where reaction at position 2 was observed exclusively with the three hard nucleophiles (Scheme 6).

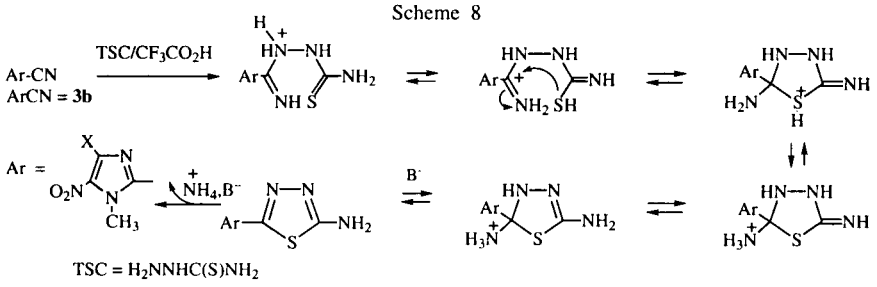
5 - Synthesis of 4-substituted megazols and of a tritiated compound.

The reference molecule was obtained by treatment of **3b** with thiosemicarbazine [19] in an acid catalyzed reaction followed by a ring closure process, the mechanism of which is suggested in Scheme 8. Substitutions were then performed on the 4-halogeno megazol.

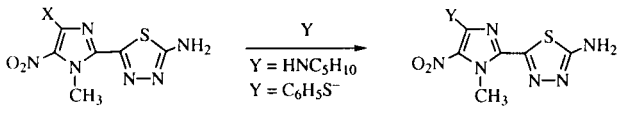
For the reasons given above, the reaction was straightforward for soft nucleophiles such as phenyl sulfide ion or amines, where the corresponding compounds were obtained quantitatively. Conversely, substitutions by fluorine or methoxide ion, hard nucleophiles, failed (Scheme 9).

Substitution at position 4 with hydride ion also failed. This result can be explained on the same grounds as those previously described. As a result the tritiated compound could not be obtained through this route. However, by replacing the bromo substituant with an iodo, through a quantitative soft-soft reaction, it was possible to obtain the desired tritiated compound; it is indeed known [16] that with an iodo group, the reaction follows a different mechanistic pathway leading to a carbanion intermediate, which is stabilized by the nitro group. Tritiation of the latter was therefore obtained from tritiated water [18] (Scheme 10).

Scheme 8



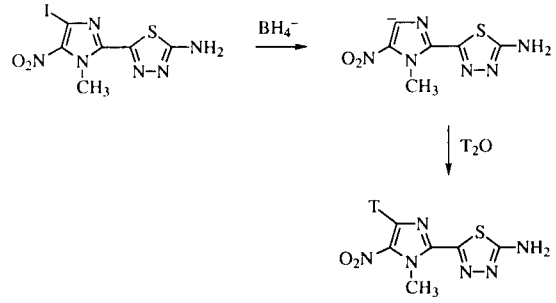
Scheme 9



4b X=Br

4e Y= NC_5H_{10}
4f Y= C_6H_5S

Scheme 10



In conclusion, the reactivity observed with substituted nitroimidazoles and the consequences for the synthesis of 4-substituted megazol analogues, can be rationalized on grounds of differences, firstly on thermodynamic stabilities of 4-versus 5-nitro imidazoles and, secondly on differences in the hard and soft character of carbons 4 and 2 in 5-nitroimidazoles. For the methylation reaction on the nitrogen of 4/5 nitroimidazole, conditions can be found where the kinetic product (5-nitro), *N*-methyl product is obtained. In the case of 2,4-dihalo-5-nitroimidazole, the conjugation of the C_4-C_5 double bond with the nitro-group renders carbon 4 soft, thereby allowing soft nucleophiles to react at this position, whereas hard nucleophiles react at carbon 2 due to weaker polarizability.

By the methods described above, 4 substituted megazol derivatives were obtained. Because nucleophilic substitution of a halogen at position 4 by hydride ion, a hard nucleophile, was ruled out, an alternative route was found to prepare the 4-tritiated megazol, needed for metabolic studies.

EXPERIMENTAL

Melting points were determined on an Electrothermal capillary melting point apparatus and were uncorrected. The IR spectra were recorded on a PerkinElmer 1610 Model FTIR. ^1H and ^{13}C nmr spectra were recorded on a Brucker AC80 (80 MHz) and AC200 (50 MHz). Chemical shifts are reported in ppm relative to tetramethyl silane as internal standard. Mass spectra were acquired on a Nermag R1010 spectrometer at Paul Sabatier University, Toulouse, France. Research chemicals were purchased from Aldrich Chemical Co and were used as supplied. Dimethylformamide and dimethyl sulfoxide were dried by storing over 4A molecular sieves.Tetrahydrofuran was distilled over sodium in presence of benzophenone ketyl as indicator prior to use. Reactions and column chromatographic separations were followed by thin layer chromatography using silicagel (with 254 nm fluorescent indicator) on aluminium plates.

2,4-dichloro-5-(4)-nitroimidazole (**1a**).

Compound **1a** was synthesized as previously described [9] by refluxing **1b** 2,4-dibromo-5-(4) nitroimidazole in concentrated hydrochloric acid, mp 175-176°, lit mp 176° [9]. ^{13}C nmr (dimethyl sulfoxide-d_6): δ 123.5 (C4), 131.6 (C2).

2,4-dibromo-5-(4)-nitroimidazole (**1b**).

Compound **1b** was prepared as described [9] by adding bromine to 5-nitroimidazole. ^{13}C nmr (dimethyl sulfoxide-d_6): δ 126.1 (C2), 120.0 (C4).

2,4-diiodo-5-nitroimidazole (**1c**).

Compound **1c** was prepared by nitration of 2,4,5-triiodoimidazole as previously described by this research group [18], mp 202-203°. ^{13}C nmr (dimethyl sulfoxide-d_6): δ 92.3 (C2), 77.6 (C4).

2,4-dichloro-1-methyl-5-nitroimidazole (**2a**).

A solution of **1a** (1.1 g, 5.6 mmoles) in tetrahydrofuran (10 ml) was added to an excess of diazomethane in ether solution at-20°. After one hour at room temperature, the solution was dried with magnesium sulfate and the solvent evaporated off under vacuum to yield a crude solid composed of 95% **2a** and 5% of the regioisomer **2'a**. The product ratio was determined by integration of the ^1H nmr signals at 3.95 and 3.70 ppm for **2a** and **2'a** respectively. ^{13}C nmr (deuteriochloroform): δ 136 (C2), 131.2 (C4), 35.7 (NCH_3); ms: (chemical ionization, ammonia) m/z 213 (M^++18, 100), 215 (M^++20, 63).

Anal. Calcd. for $C_4H_3Cl_2N_3O_2$: C, 24.51; H, 1.51; N, 21.44. Found: C, 24.72; H, 1.62; N, 21.53.

2,4-dibromo-1-methyl-5-nitroimidazole (**2b**).

Compound **2b** was obtained by mixing **1b** (2.7 g, 10 mmoles) with diazomethane (20 mmoles, 25 ml), yield 2.7 g of **2b**, mp 160-161°. ^1H nmr (deuteriochloroform): δ 4.00; ^{13}C nmr (deuteriochloroform): δ 137.1 (C5), 126.0 (C2), 119.6 (C4), 37.6 (NCH_3); ms: (chemical ionization, ammonia) m/z 284 (M^++1, 52), 286 (M^++3, 100), 288 (M^++5, 50).

2,4-diiodo-1-methyl-5-nitroimidazole (**2c**).

Compound **2c** was prepared by the same method used for **2a** and **2b** starting from **1c** (1.7 g, 4 mmoles) in tetrahydrofuran with diazomethane, giving a quantitative conversion to 95% **2c** and 5% **2'c**, mp 189-190°. ^1H nmr (dimethyl sulfoxide-d_6): δ 4.06 and 3.73 for **2'c**; ^{13}C nmr (dimethyl sulfoxide-d_6): δ 141.9 (C5), 107.7 (C2), 93.8 (C4), 39.0 (NCH_3); ms: (chemical ionization, ammonia) m/z 380 (M^++1, 100).

Anal. Calcd. for $C_4H_3I_2N_3O_2$: C, 12.66; H, 0.79; N, 11.08. Found: C, 12.57; H, 0.82; N, 11.14.

Analysis and separation of mixtures of regiomers **2b** 2,4-dibromo-1-methyl-5-nitro imidazole and **2'b** 2,5-dibromo-1-methyl-4-nitroimidazole.

The same procedure as for that described below, with dimethyl sulfate, was adopted for extraction and separation in experiments mentioned in Table 1.

A mixture of **1b** (2.7 g, 10 mmoles) dimethyl sulfate (1 ml) and dioxane (10 ml) was refluxed for 18 hours. The solvent was evaporated off under vacuum and the residual oil was treated with a saturated solution of hydrogenocarbonate (2 x 10 ml) and extracted with dichloromethane (3 x 20 ml). After drying (magnesium sulfate) and vacuum evaporation, a solid mixture of

2b and **2'b** (1 g) was separated by flash chromatography (silicagel) with dichloromethane-petroleum ether (1:1) as the eluent giving 400 mg each of **2b** and **2'b**, mp 204-205°. ^{1}H nmr (deuteriochloroform): δ 3.78; ^{13}C nmr (deuteriochloroform): δ 145.2 (C4), 120.5 (C2), 106.6 (C5), 35.1 (NCH_3); ms: (chemical ionization, ammonia) m/z 301 (M^++18, 47), 303 (M^++20, 100), 305 (M^++22, 47).

Anal. Calcd. for $C_4H_3Br_2N_3O_2$: C, 16.86; H, 1.06; N, 14.75. Found: C, 16.81; H, 1.03; N, 14.68.

4-chloro-2-cyano-1-methyl-5-nitroimidazole (**3a**).

Compound **2a** (1 g, 5 mmoles) was mixed with potassium cyanide (440 mg, 7 mmoles) and 18-crown-6 (50 mg) in dimethyl sulfoxide (5 ml) and heated at 80° for 18 hours. After the usual work up, purification by flash chromatography, ethyl acetate-petroleum ether (1:3), pure **3a** was obtained (660 mg, 3.5 mmoles). ^{1}H nmr (deuteriochloroform): δ 4.15; ^{13}C nmr (deuteriochloroform): δ 133.2 (C4), 122.3 (C2), 108.5 (CN), 37.2 (NCH_3); ms: (chemical ionization, methane) m/z 187 (M^++1, 100), 189 (M^++2, 40); ir (potassium bromide): 2246 cm^{-1} (CN).

4-bromo-2-cyano-1-methyl-5-nitroimidazole (**3b**).

The same process as that described for **3a** was applied. A mixture of **2b** (285 mg, 1 mmole), potassium cyanide (70 mg, 1.1 mmoles), 18-crown-6 (20 mg) in dimethyl sulfoxide (2 ml) was heated for 2 hours at 80° giving 200 mg (85% yield) of **3b** after workup and purification by chromatography, mp 101°. Ir (potassium bromide): 2247 cm^{-1} (CN); ^{1}H nmr (deuteriochloroform): δ 4.18; ^{13}C nmr (deuteriochloroform): δ 137.1 (C5), 124.0 (C2), 120.1 (C4), 108.2 (CN), 37.3 (NCH_3); ms: (electronic impact) m/z 230 (M^+, 20), 232 (M^++2, 20).

Anal. Calcd. for $C_5H_3BrN_4O_2$: C, 25.99; H, 1.31; N, 24.25; O, 13.85. Found: C , 26.10; H, 1.23; N, 24.30.

2-cyano-4-iodo-1-methyl-5-nitroimidazole (**3c**).

Compound **2c** (378 mg, 1 mmole) was mixed with potassium cyanide (80 mg, 1.2 mmoles) and 18-crown-6 ether (10 mg) in dimethylformamide (3 ml) and heated for 2 hours at 80° affording 120 mg of **3c** (45% yield) after the usual work up and chromatography; mp 111-112° ir (potassium bromide): 2245 cm^{-1} (CN). ^{1}H nmr (deuteriochloroform): δ 4.18; ^{13}C nmr (deuteriochloroform): δ 126.7 (C2), 108.5 (CN); 89.2 (C4), 37.3 (NCH_3); ms: (chemical ionization, ammonia) m/z 279 (M^++1, 100), (M^++18, 12).

Anal. Calcd. for $C_5H_3IN_4O_2$: C, 21.60; H, 1.09; N, 20.15. Found: C, 21.35; H, 1.10; N, 20.30.

4-bromo-2-methoxy-1-methyl-5-nitroimidazole (**3d**).

Compound **3b** (285 mg, 1 mmole) along with sodium methoxide (57 mg, 1.1 mmoles) was refluxed in methanol (5 ml) for 3 hours. After vacuum evaporation of methanol, the solid residue was dissolved in water (5 ml) extracted with dichloromethane (2 x 10 ml). The resulting solid was eluted by flash chromatography (dichloromethane) to afford **3d** (200 mg) as yellow cristalline needles, mp 89°. ^{1}H nmr (deuteriochloroform): δ 4.11 (s) and 3.71 (s); ^{13}C (deuteriochloroform): δ 152.0 (C2), 132.1 (C5), 116.2 (C4), 57.9 (OCH_3), 32.3 (NCH_3); ms: (chemical ionization, ammonia) m/z 236 (M^++1, 25), 238 (M^++3 , 25), 253 (M^++18, 100), 255 (M^++20, 100).

Anal. Calcd. for $C_5H_6BrN_3O_3$: C, 25.44; H, 2.56; N, 17.80. Found C, 25.30; H, 2.70; N, 17.67.

4-bromo-1-methyl-5-nitroimidazole (**3e**).

Compound **2b** (140 mg, 0.5 mmole) in presence of sodium borohydride (30 mg, 0.8 mmole) dissolved in dimethyl sulfoxide containing 20% water (2 ml) and heated at 80° one hour. The mixture was poured into water (15 ml) and the aqueous phase extracted with dichloromethane (2 x 10 ml), dried (magnesium sulfate) and purified by flash chromatography using ethyl acetate-petroleum ether (1:1) as the eluent to afford 80 mg of **3e**, (80% yield); mp 103-104°, mp lit 104° [15]. ^{1}H nmr (deuteriochloroform): δ 7.5 (H2), 4.0 (NCH_3); ^{13}C (deuteriochloroform): δ 120 (C4), 36.8 (NCH_3); ms: (chemical ionization, ammonia) m/z 206 (M^++1, 100), 208 (M^++3, 100), 223 (M^++18, 90), 225 (M^++20, 90).

2-bromo-5-cyano-1-methyl-4-nitroimidazole (**3'b**).

Under the conditions previously described for **3b**, **2'b** (285 mg, 1 mmole) potassium cyanide (80 mg, 1.2 mmoles) and 18-crown-6 ether (10 mg) are mixed in dimethyl sulfoxide (3 ml) and heated at 80° for 24 hours producing, after the usual work up; 20 mg (10% yield) of **3'b**. ^{1}H nmr (dimethyl sulfoxide-d_6): δ 3.78; ^{13}C nmr (dimethyl sulfoxide-d_6): δ 149 (C4), 125.4 (C2), 108 (CN), 106 (C5), 35.5 (NCH_3), ir (potassium bromide): 2245 cm^{-1}; ms: (chemical ionization, ammonia) m/z 231 (M^++1, 100), 233 (M^++3, 100).

2-bromo-1-methyl-4-nitroimidazole (**3'e**).

Compound **2'b** (140 mg, 0.5 mmole) was reacted with sodium borohydride under the same conditions as that described for **2b** to give **3'e** (50 mg, 0.24 mmole) as white crystals, mp 152°, (lit mp 143-145° [19]). ^{1}H nmr (deuteriochloroform): δ 7.8 (H5), 3.7 (NCH_3); ms: (chemical ionization, ammonia) m/z 206 (M^++1, 9), 208 (M^++3, 9), 223 (M^++18, 100), 225 (M^++20, 100).

2-bromo-5-methoxy-1-methyl-4-nitroimidazole (**3'd**).

A mixture of **2'b** (280 mg, 1 mmole) and sodium methoxide (70 mg, 1.1 mmoles) was refluxed in methanol for 8 hours affording, after the usual work up, 80 mg of **3'd** (40% yield). ^{1}H nmr (deuteriochloroform): δ 4.18 (s), 3.46 (s); ^{13}C nmr (deuteriochloroform): δ 113.8 (C2), 63.8 (OCH_3), 31.3 (NCH_3).

4-bromo-2-(1-methoxyimino)-1-methyl-5-nitroimidazole **3f**.

A mixture of compound **3b** (300 mg, 1.3 mmoles), sodium methoxide (80 mg, 1.4 mmoles) and methanol (5 ml) was stirred for half an hour at room temperature at which time tlc analysis showed that **3b** had disappeared. After methanol evaporation, addition of water (10 ml), extraction with dichloromethane (2 x 10 ml) and flash chromatography using ethyl acetate-petroleum ether (1:4) as the eluent, 40 mg of **3d** and 170 mg of **3f** (0.64 mmole) were isolated. ^{1}H nmr (deuteriochloroform): δ 4.18 (NCH_3), 4.00 (OCH_3); ^{13}C nmr (deuteriochloroform): δ 158.4 (C=N), 139.8 (C2), 119 (C4), 54.4 (OCH_3); 36.7 (NCH_3); ms: (chemical ionization, ammonia) 264 (M^++1, 71), 266 (M^++3, 70), 281 (M^+18, 39), 283 (M^++20, 39).

2-amino-5-(1-methyl-4-bromo-5-nitro-2-imidazolyl)-1,3,4-thiadiazol (**4b**).

Compound **3b** (564 mg, 2 mmoles) was heated for 15 hours at 50° in trifluoroacetic acid (5 ml) and thiosemicarbazide (191 mg, 2.1 mmoles). After evaporation of trifluoroacetic acid under vacuum, the compound was neutralized with sodium hydrogenocarbonate solution (2 x 5 ml) washed with water (5 ml), and ether

(5 ml) then dried at 40° under vacuum to give 500 mg of **4b** (1.7 mmoles), mp 260° dec. ^{1}H nmr (dimethyl sulfoxide-d_6): δ 4.30; ^{13}C nmr (dimethyl sulfoxide-d_6): δ 170 (C-NH_2), 147 (C2'), 140 (C2), 136.9 (C5), 119.6 (C4), 36.2 (NCH_3); ms: (chemical ionization, ammonia) m/z 305 (M+1, 10), 307 (M+3, 10), 322 (M+18, 12), 324 (M+20, 12).

Anal. Calcd. for $C_6H_5BrN_6O_2S$: C, 23.75; H, 1.65; N, 27.50. Found: C, 23.32; H, 1.58; N, 27.35.

2-amino-5-(1-methyl-4-iodo-5-nitro-2-imidazolyl)-1,3,4-thiadiazol (**4c**).

Compound **3c** (278 mg, 1 mmole) was submited to the same conditions and work up as that described for **3b** in the synthesis of **4b**. Under those conditions 250 mg of **4c** (0.8 mmole) was obtained. ^{13}C nmr (dimethyl sulfoxide-d_6): δ 170 (CNH_2), 147 (C'2), 141 (C2), 133 (C5), 93 (C4), 36.2 (NCH_3); ms: (chemical ionization, ammonia) m/z 353 (M^+1, 100).

2-amino-5-(1-methyl-5-nitro-4-piperidino-2-imidazolyl)-1,3,4-thiadiazol (**4e**).

A mixture of compound **4b** (150 mg, 0.5 mmole) and piperidine (0.5 ml, 8 mmoles) was stirred in tetrahydrofuran (20 ml) for 5 hours at room temperature, and gave **4e** (110 mg, 0.7 mmole) after the usual work up described previously. ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.85 (NH_2), 4.22 (NCH_3), 3.42 (NCH_2-), 1.63 (CH_2); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 170 (CNH_2), 153 (C'4), 147.9 (C45), 139.6 (C2), 36.2 (NCH_3), 25.2 (NCH_2), 23.6 (CH_2); ms: (chemical ionization, ammonia) m/z 310 (M^++1, 100).

Anal. Calcd. for $C_{11}H_{15}N_7O_2S$: C, 42.63; H, 4.87; N, 31.80. Found: C, 42.47; H, 4.65; N, 31.35.

2-amino-5-(1-methyl-5-nitro-4-thiophenyl-2-imidazolyl)-1,3,4-thiadiazol (**4f**).

A mixture of compound **4b** (150 mg, 0.5 mmoles) thiophenol (0.3 ml, 3 mmoles) sodium methoxide (100 mg, 2 mmoles) in tetrahydrofuran (20 ml) were stirred for 15 hours at room temperature, and after following the previous process obtained **4f** (170 mg, 90% yield), mp 275°. ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.56 (NH_2), 7.46 (C_6H_5), 4.30 (NCH_3); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 170.2 (CNH_2), 147.6 (C'2), 140.8 (C2), 134.2 (C_6H_5, m), 129.2 (C_6H_5, p), 129.0 (C_6H_5, o), 128.2 (C4), 35.5 (NCH_3); ms: (chemical ionization, ammonia) m/z 335 (M^++1, 100).

Anal. Calcd. for $C_{12}H_{10}N_6O_2S_2$: C, 43.1; H, 2.99; N, 25.13. Found: C, 42.97; H, 3.1; N, 23.5.

2-cyano-1-methyl-5-nitro-4-trifluoromethylimidazole (**5**).

In a Schlenck tube equipped with refrigerant and magnetic bar, cuprous iodide (4.25 g, 25 mmoles), **3b** (924 mg, 4 mmoles) were diluted in degassed hexamethyl phosphoramide (10 ml), and an excess of trifluoromethylcadmium bromide (10 mmoles, 10 ml dimethylformamide) prepared by the Burton method [17] was introduced under argon by syringe. This mixture was heated for 6 hours at 70°. After cooling, it was filtered under vacuum on cintered glass to eliminate metallic salts and poured into water (100 ml). Extraction with dichloromethane (4 x 30 ml) and the usual work up gave an orange oil that was purified by flash chromatography (ether-hexane:1-1) to afford **5** as orange crystals (570 mg, 60% yield), mp 85-86°. ^{1}H nmr (deuteriochloroform): δ 4.19 (NCH_3); ^{13}C nmr (deuteriochloroform): δ 122.9 (C2), 118.6 (CF_3 q , $^1J_{CF3}$ 270 Hz), 108.2 (CN), 36.5 (NCH_3); ms: (electronic impact) m/z 220 (M^+, 20).

Anal. Calcd. for $C_6H_3F_3N_4O_2$: C, 32.74; H, 1.3; N, 25.45. Found C, 32.67; H, 1.41; N, 25.38.

2-cyano-1-methyl-5-nitro-4-thiophenylimidazole (**6**).

In a flask under argon, a thiophenol solution in tetrahydrofuran (110 mg, 1 mmole, 2 ml) was added to a tetrahydrofuran sodium hydride suspension (30 mg, 1 mmole, 2 ml) until hydrogen evolution ceased, at which time **2b** diluted in tetrahydrofuran (230 mg, 1 mmole, 2 ml) was added by syringe. After 18 hours agitation at room temperature, the mixture was evaporated to dryness, water was added (10 ml) and the product ectracted with dichloromethane (2 x 10 ml) followed by the usual work up and chromatography (ethylacetate-hexane:1-4) to give **6** as yellow crystals (200 mg, 75% yield), mp 100-101°. ^{1}H nmr (deuteriochloroform): δ 4.14 (NCH_3), 7.48 (phenyl); ^{13}C nmr (deuteriochloroform): δ 135.3 (C_6H_5, m), 130.2 (C_6H_5, p), 129.6 (C_6H_5, o), 127.0 (C4), 124.8 (C2), 100.1 (CN), 36.4(NCH_3).

Anal. Calcd. for $C_{11}H_8N_4O_2S$: C, 50.70; H, 3.10; N, 21.53. Found: C, 50.60; N, 21.15; H, 3.12.

4-thiomethyl-2-(1-methoxyimino-1-methyl-5-nitroimidazole (**7**).

Compound **3b** (640 mg, 2.8 mmoles) was dissolved in a tetrahydrofuran ammonia solution (25 ml NH_3 35%, 75 ml THF), and dihydrogen sulfide was bubbled in this orange solution forming a red precipitate (1 g) non characterised nmr (dimethyl sulfoxide-d_6) unresolved, probably ammonium salt of the 4-thiol substitute of **3b**. This ammonium sulfide (400 mg, 2 mmoles) was heated with potassium *tert*-butoxide (380 mg, 3.6 mmoles) and methyl iodide (0.160 ml, 2.2 mmoles) in methanol (5 ml) at 60° for 2 hours. After vacuum evaporation, dissolution in water (20 ml) extraction in dichloromethane and flash chromatography (ethyl acetate-petroleum ether: 1-4), **7** was isolated (150 mg, 0.65 mmole, 30% yield). ^{1}H nmr (deuteriochloroform): δ 4.17 (NCH_3), 3.99 (OCH_3), 2.57 (SCH_3); ^{13}C (deuteriochloroform): δ 159.5 (C=N), 148 (C4), 140.0 (C2), 54.3 (OCH_3), 36.0 (NCH_3), 13.7 (SCH_3); ms: (chemical ionization, ammonia) m/z 231 (M^++1, 100).

Anal. Calcd. for $C_7H_{10}N_4O_3S$: C, 36.51; H, 4.38; N, 24.33. Found: C, 36.47; H, 4.41; N, 24.25.

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