SYNTHESIS OF 4-HIGHLY BRANCHED IMIDAZOLE DERIVATIVES VIA CINE-SUBSTITUTION AND $S_{RN}1$ SUBSTITUTION OF 5-NITROIMIDAZOLES WITH ANIONS OF NITROALKANES[§]

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Abstract ——— Cine-substitution and $S_{RN}1$ substitution of 1,2-dimethyl-5-nitroimidazole with the anions of secondary nitroalkanes provide a new and rapid synthesis of 4-highly branched imidazole derivatives in good yields. The mechanistic aspects of the involved reactions are discussed.

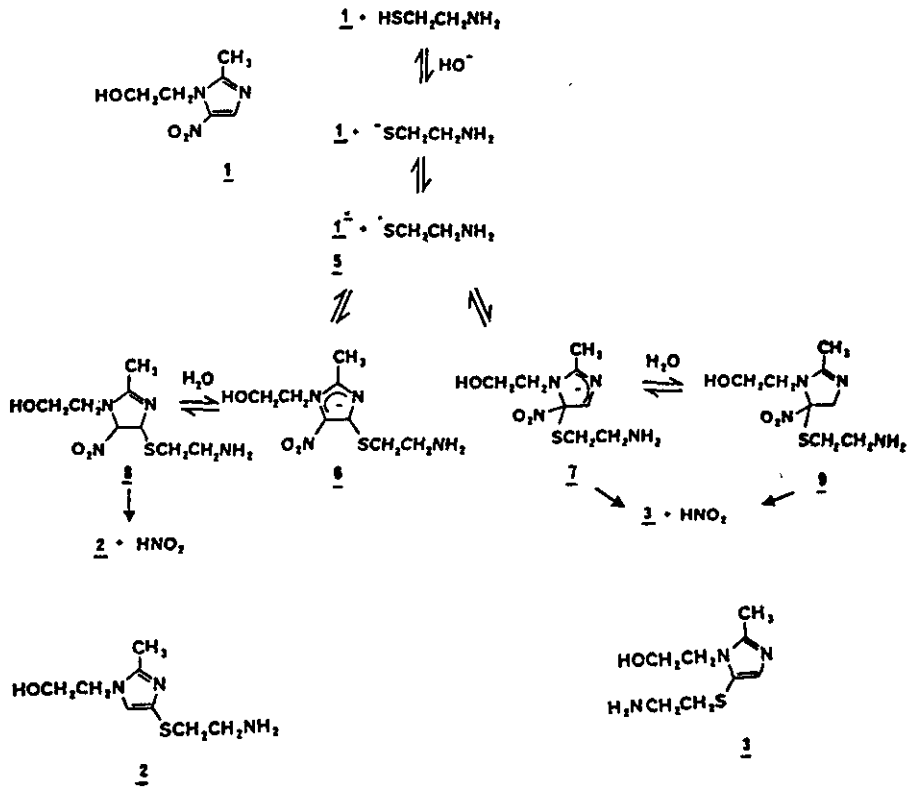
Metronidazole (1) and other 5-nitroimidazole derivatives are used extensively to treat infections caused by anaerobic protozoa and bacteria.[1] Observations that important biological effects of nitroimidazoles are associated with reductive metabolism[2] have led to considerable interest in nitroimidazole reduction chemistry. Several types of evidence strongly suggests that the mechanism of biological action involves their reduction to radical anions,[3] nitrosoimidazoles[4] or hydroxylaminoimidazoles and that one of these partially reduced metabolites causes biological activity by reacting with targets like cellular DNA. This hypothesis is supported by a series of reactions of metronidazole with 2-aminoethanethiol, which may be considered analogous to the biologically important nucleophile glutathione.

The reaction of metronidazole with excess thiol under N_2 (H_2O, 100°C, 1.5 h) produced 4-[(2-aminoethyl)thio]-2-methylimidazole-1-ethanol (2) in 98% yield.[3] The formation of this cine-substitution product can be explained by electron transfer from thiolate, coupling of the radical anion of metronidazole with the thiyl radical to give the Meisenheimer complex, protonation and nitrous acid elimination as described in Scheme 1.

Recently, it has been shown that α-nitrofurans bearing acyl of alkoxycarbonyl groups on the α'-position react with the anions of secondary nitroalkanes to give the cine-substitution products regioselectively.[5] This high regioselectivity is only observed when the anions of nitroalkanes are used as nucleophiles. In these examples the resulting tertiary nitro compounds have not been reported to react further by $S_{RN}1$ substitution with an excess of nitronate anions.

[§]This paper is respectfully dedicated to Sir Derek Barton on the occasion of his 70th birthday.

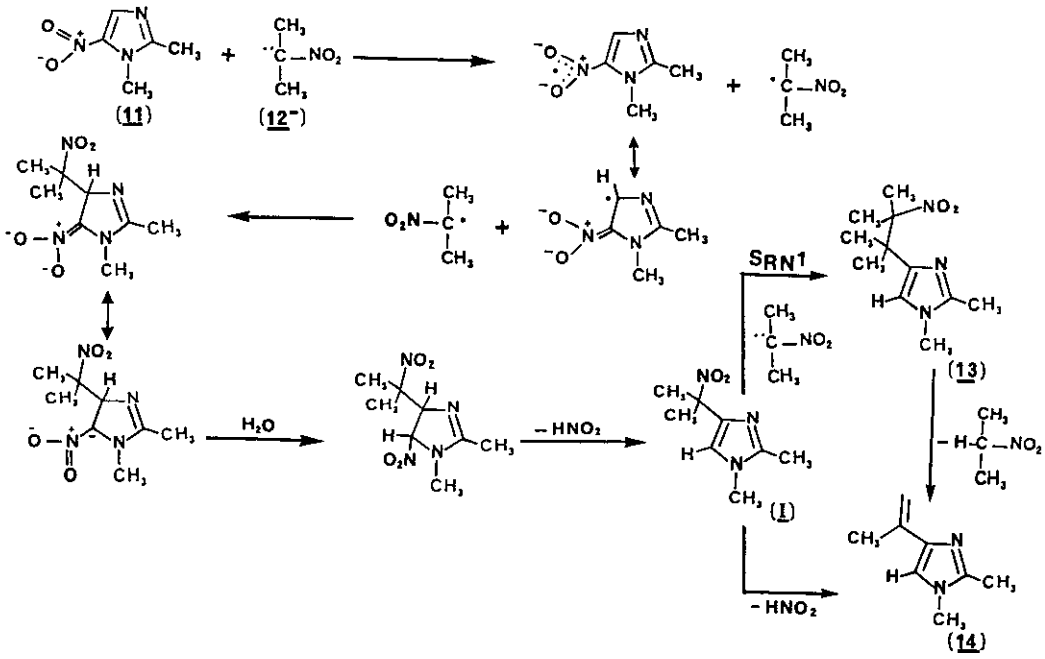
SCHEME 1



As a part of our studies on the substitution reactions of nitroimidazole compounds,[6] the reaction of 1,2-dimethyl-5-nitroimidazole (11) (Emtryl^{R}) with the salts of secondary nitroalkanes, such as 2-nitropropane and nitrocyclohexane was examined. In this paper, we report a new and rapid synthesis of 4-highly branched imidazole derivatives, which are important new synthons in the *preparation of* histamine derivatives and in the developement of potentially safer nitroimidazoles.[7] In an attempt to prepare an imidazole analog of α-nitrocumene by cine-substitution in order to study its reactivity in $S_{RN}1$ reactions, we warmed under argon atmosphere a solution of dimetridazole (11) in toluene and excess tetrabutylammonium salt of 2-nitropropane (12) in water (19 h, reflux). A reaction occurred giving two products that could be separated by solubility differences and column chromatography : 1,2-dimethyl-4-(1,1,2-trimethyl-2-nitropropyl) imidazole (13) (64%) and 1,2-dimethyl-4-(1-methylvinyl) imidazole (14) (16%). A much less expansive reaction, using sodium salt of 2-nitropropane and phase-transfer catalysis by tetrabutylammonium bromide gave similar results (13) (61%) and (14) (14%). The formation of the products (13) and (14) can involve the reactions summarized in Scheme 2. Previous works have shown that nitronate anions react by $S_{RN}1$ mechanism with 5-nitroimidazoles bearing a leaving group on the methylene groupe at position 2.[6,8]

The first step of this reaction is an electron transfer from the nitronate anion to the 5-nitroimidazole giving the 2-nitropropyl radical and the radical anion of the 5-nitroimidazole. When the starting material is of the type of 1-methyl-2-chloromethyl-5-nitroimidazole, the corresponding radical anion gives a fragmentation leading to the 1-methyl-5-nitroimidazolylmethyl radical and loss of chloride ion. If the 5-nitroimidazole has no leaving group, the corresponding radical anion has now the possibility to react with the 2-nitropropyl radical to give a Meisenheimer complex. Single electron transfer in aromatic nucleophilic addition and substitution has been discussed in details[9] and it has been demonstrated that in relatively aqueous solvents charge-transfer complexes between radical anions and radicals of the nucleophiles are probable intermediates in nucleophilic aromatic addition and substitution.

SCHEME 2

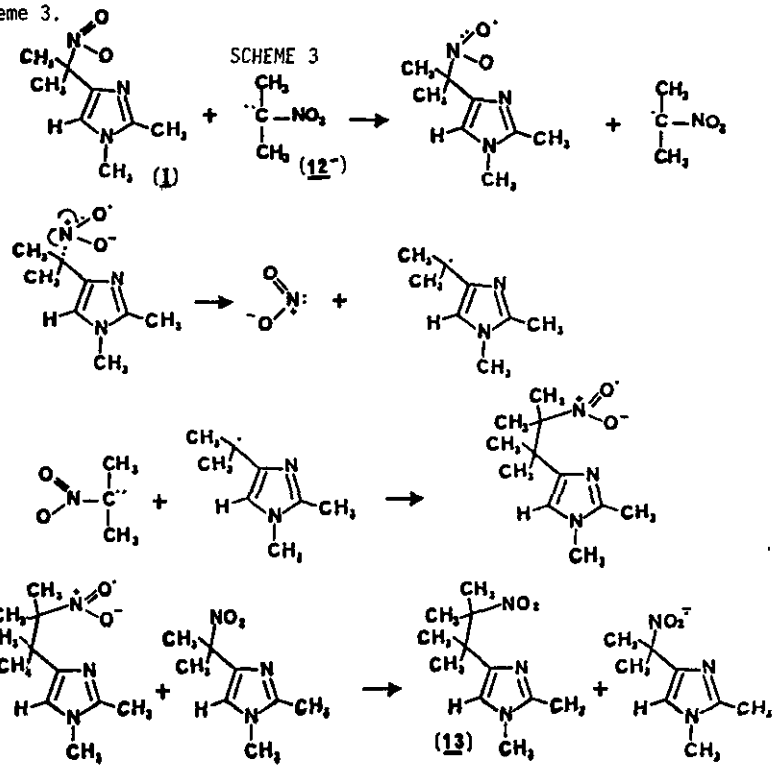


A selective coupling of the radical anion and the 2-nitropropyl radical to give the formation of a C-C bond into position 4 also is in agreement with ESR studies of the dimetridazole radical anion from which it is possible to calculate that 20% of the spin density is localized at C_4.[10] The intermediate cine-substitution product (I) is not isolated in these reactions even with low conversion of dimetridazole or if the reaction is carried out at lower temperature (CH_2Cl_2, reflux or DMSO, room temperature). The formation of the compound (14) from this hypothetical intermediate

can be explained by nitrous acid elimination. We have shown in a blank experiment that (13) is not the precursor of (14) in the reaction conditions (tetrabutylammonium salt of 2-nitropropane in excess, H_2O-toluene, reflux, 24 h) and it is possible to conclude that the cine-substitution product (I) is the reactive intermediate. In connection with this, we have considered the possibility of a base-promoted addition of 2-nitropropane on (14) leading to (13). This reaction is not observed. The cine-substitution product (I) being the key intermediate of this reaction, its reactivity with nitronate anions may appear quite surprising owing to the fact this tertiary nitro compound has no other electron-withdrawing group other than imidazole ring. Two related examples of $S_{RN}1$ substitution with nitrogen heterocyclic compounds without other electron-withdrawing group have been shown to give good yields of substitution products with 2-nitropropane anion. The first example is the reaction of 2-nitro-2-(4-pyridinyl)propane which gave the corresponding $S_{RN}1$ product in 86% yield.[11] The second example is the reaction of 2-(1-imidazolyl)-2-nitropropane which gave 65% yield of the $S_{RN}1$ product.[12] However, neither of these works has reported the formation of an ethylenic compound resulting of nitrous acid elimination from the starting tertiary nitro compound.

We propose that the cine-substitution product (I) is the reactive intermediate which can lose nitrous acid to give the ethylenic compound (14) and that all the data provide good evidence for assigning $S_{RN}1$ mechanism to the formation of the 4-highly branched imidazole derivative (13) as fully illustrated by Scheme 3.

SCHEME 3



Concerning the structure of (13), it is noteworthy than in spite of extensive studies by X-ray analysis, the structure of this compound has been impossible to find from calculations. The structure of (13) has been confirmed by Bu_3SnH reduction, the nmr spectrum showing the thexyl group at position 4, by hydrolysis and X-ray determination of the structure of the corresponding tertiary alcohol, by $S_{RN}1$ reaction with nitromethane anion and by $LiAlH_4$ reduction giving the corresponding tertiary amine with the histamine skeleton. The radical deamination of this amine by Barton reaction[13] is currently being explored. All these results which are in progress will be published elsewhere. Finally, we have found that (13) can be quantitatively transformed into compound (14) by 2-nitropropane loss simply when subjected to column chromatography on alumina (Merck aluminium oxide 90 active, neutral for column chromatography). Elution with methylene chloride then with methanol afforded pure (14). The mechanism of this elimination is unknown but we have observed that the reaction is very sensitive to the quality of alumina and the structure of the substrate (i.e., the basicity of the imidazole) because when the analogous 5-nitro derivative is treated in the same conditions, this compound is recovered unchanged without 2-nitropropane elimination.

In conclusion, we have found that 5-nitroimidazoles react with nitroalkane anions to give via cine-substitution a tertiary nitro intermediate which can lose nitrous acid or undergo $S_{RN}1$ substitution with nitronate anions. This new and rapid synthesis of 4-highly branched imidazole derivatives opens the way to the preparation of new compounds with the histamine skeleton. These compounds also after nitration could be used for developing nonmutagenic 5-nitroimidazoles of great interest. Several interesting mechanistic aspects of reactivity related to an intramolecular catalysis by imidazole also are discernable, the compound (13) exhibiting a double gem-dimethyl effect and a perfect molecular structure for an intramolecular assistance. Finally, the synthesis of (14) an α-methylstyrene-like compound permits to imagine many free radical reactions[14] useful to synthesis of complex target molecules of biological interest.

ACKNOWLEDGEMENTS

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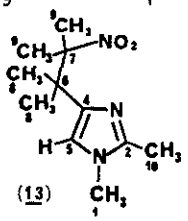
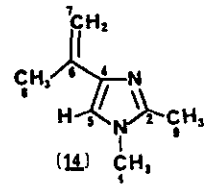
EXPERIMENTAL

General Procedure for Reactions of 1,2-Disubstituted 5-Nitroimidazoles (11) with Tetrabutylammonium Salts of Nitroalkanes (12) [Preparation of 1,2-Dimethyl-4-(1,1,2-trimethyl-2-nitropropyl) imidazole (13) as an Example]----- Under argon atmosphere, an aqueous solution of

tetrabutylammonium hydroxide 40% in water (25.97 g, 40 mmol) was reacted with 2-nitropropane (12) (3.56 g, 40 mmol) for 1 h. A solution of 1,2-dimethyl-5-nitroimidazole (Dimetridazole or Emtryl^{R}) (11) (1.41 g, 10 mmol) in 40 ml of toluene was added and the mixture was stirred and refluxed for 19 h. After cooling, the organic layer was separated and the aqueous layer was extracted with three portions of toluene (50 ml). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was fractionated by silica gel column chromatography. Elution with $CHCl_3/CH_3OH$ (9/1) afforded 1.43 g (64%) of (13) and 0.22 g (16%) of 1,2-dimethyl-4-(1-methylvinyl)imidazole (14). (13) was purified by recrystallization from pentane. Colorless needles mp 115°C. Anal. Calcd for $C_{11}H_{19}N_3O_2$: C, 58.64 ; H, 8.50 ; N, 18.65. Found ; C, 58.60 ; H, 8.51 ; N, 18.63. Ir (solid) : 1534 cm^{-1} (NO_2). ^{1}H-Nmr ($CDCl_3$) δ ppm : 1.38 (s, 6H), 1.60 (s, 6H), 2.30 (s, 3H), 3.47 (s, 3H) , 6.47 (s, 1H). ^{13}C-Nmr ($CDCl_3$) δ ppm : 12.83 (C_{10}), 23.41 (C_8), 23.81 (C_9), 32.68 (C_1), 41.11 (C_6), 94.84 (C_7), 117.53 (C_5), 143.53 (C_2), 143.64 (C_4).



(13)



(14)

Ms (70 ev) m/z (%) : 225 (1.3), 179 (4.4), 163 (7.7), 137 (100), 122 (3.3), 109 (2.6), 94 (2.4), 81 (5.5), 68 (4.6), 56 (14.1), 42 (14.4), 30 (5.3).

(14) was purified by Kugelrohr distillation $bp_{5.25}$ 150°C. Ir (liquid) : 1635 cm^{-1} ($H_2C=C$). ^{1}H-Nmr ($CDCl_3$) δ ppm : 2.0 (s, 3H), 2.37 (s, 3H), 3.47 (s, 3H), 4.80 (broad s, 1H), 5.57 (broad s, 1H), 6.67 (s, 1H). ^{13}C-Nmr ($CDCl_3$) δ ppm : 12.81 (C_9), 20.29 (C_8), 32.76 (C_1), 108.69 (C_7), 116.94 (C_5), 135.94 (C_4), 140.75 (C_2), 145.93 (C_6). Ms (70 eV) m/z (%) : 137 (10.1), 136 (100), 135 (33.5), 121 (25.8), 110 (2.0), 94 (27.5), 80 (14.6), 67 (7.6), 56 (48.5), 42 (50.7), 27 (12.2).

Preparation by the Same Procedure of 1-Nitro-1'-(1,2-dimethyl-4-imidazolyl)-1:1'-bicyclohexane (15) and 1,2-Dimethyl-4-(1-cyclohexenyl) imidazole (16) ----- By the same procedure, using an aqueous solution of tetrabutylammonium hydroxide 40% in water (46 g, 71 mmol), nitrocyclohexane (9.15 g, 71 mmol) and (11) (2.50 g, 17.7 mmol) in toluene (100 ml). Elution with $CHCl_3$/acetone (7/3) afforded 3.24 g (60%) of (15) and 0.56 g (18%) of (16).

(15) was purified by recrystallization from cyclohexane. Colorless needles, mp 193°C. Anal. Calcd for $C_{17}H_{27}N_3O_2$: C, 66.85 ; H, 8.91 ; N, 13.76. Found : C, 66.94 ; H, 8.76 ; N, 13.69. ^{1}H-Nmr ($CDCl_3$) δ ppm : 1.0-2.8 (m, 20H), 2.36 (s, 3H), 3.53 (s, 3H), 6.48 (s, 1H).

(16) light yellow viscous oil. ^{1}H-Nmr ($CDCl_3$) δ ppm : 1.2-2.4 (m, 8H), 2.36 (s, 3H), 3.38 (s, 3H), 6.37 (broad s, 1H), 6.61 (s, 1H).

General Procedure for Reactions of 1,2-Disubstituted 5-Nitroimidazoles (11) with Sodium Salts of Nitroalkanes (12) under Phase-Transfer Catalysis Conditions-----Under argon atmosphere, sodium hydroxide (1.6 g, 40 mmol) in water (10 ml) was stirred with 2-nitropropane (3.56 g, 40 mmol) for 1h. A solution of 1,2-dimethyl-5-nitroimidazole (11) (1.41 g, 10 mmol) in toluene (20 ml) and tetrabutylammonium bromide (0.32 g, 1 mmol) were added and the mixture was refluxed for 24 h. The treatment already described gave (13) (61%) and (14) (14%).

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