SYNTHESIS OF 2-METHYL-4(5)-NITRO[$^{15}N^{1(3)}$]IMIDAZOLE FROM 2-METHYL-4(5)-NITROIMIDAZOLE

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SUMMARY

A simple four-stage conversion of 2-methyl-4(5)-nitroimidazole to 2-methyl-4(5)-nitro[$^{15}N^{1(3)}$]imidazole is reported. The method consists in N-nitration of the initial compound to 2-methyl-1,4-dinitroimidazole, treating the latter with [^{15}N]glycine and N-dealkylation of the obtained (2-methyl-4-nitro[$^{15}N^{1}$]imidazol-1-yl)acetic acid through its bromination in the presence of phosphorus trichloride, followed by the hydrolysis of the non-isolated intermediate.

Key words: [^{15}N]labelled nitroimidazoles, synthesis, N-dealkylation.

INTRODUCTION

Tautometric 2-methyl-4(5)-nitroimidazole alkylated with alkyl halides or sulfonates[1], epoxides[2], aziridines[3] or with some alkene derivatives[4] yields mixtures of 1-alkyl-2-methyl-4-nitro and 1-alkyl-2-methyl-5-nitroimidazoles with the dominance of one of the isomers depending on the medium used for the reaction. Both groups of compounds show considerable antitrichomonal, antiamoebic, antigiardial, antihistomonal and antibacterial activity[5]. Some of them can serve as immunosuppressants[6] or cancer cell radiosensitizers[7,8]. A number of their representatives such as Dimetridazole, Metronidazole, Panidazole, Ronidazole (5-nitroderivatives) or Isometronidazole (4-nitroderivative) are commercially available drugs. In the investigation of the metabolism of these compounds, labeling with radioactive carbon[9] has been used.

We present in this work a simple synthesis of 2-methyl-4(5)-nitro[$^{15}N^{1(3)}$]imidazole from commercially available compounds. The presence of ^{15}N in a strictly defined position of the title

CCC 0362–4803/96/040395–07

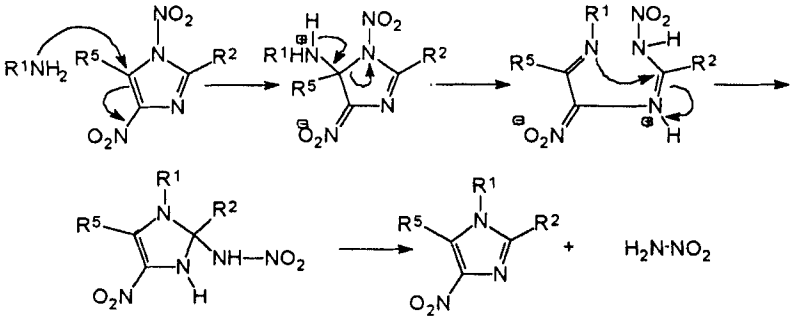
Received 16 November 1995
Revised 11 December 1995

compound may be utilised in structural investigations and in investigations of the metabolism of many 5-nitro or 4-nitroimidazole drugs and other compounds obtainable from the labelled 2-methyl-4(5)-nitroimidazole.

DISCUSSION

In 4-nitroimidazoles substituted at the 1-position with electronoacceptors such as acyl, alkanesulfonyl, arenesulfonyl or nitro groups, two centres susceptible to an attack of nucleophilic reagents are present[10]. They are an exocyclic atom combined with the ring nitrogen atom in the 1-position and the carbon atom in the 5-position of the imidazole ring.

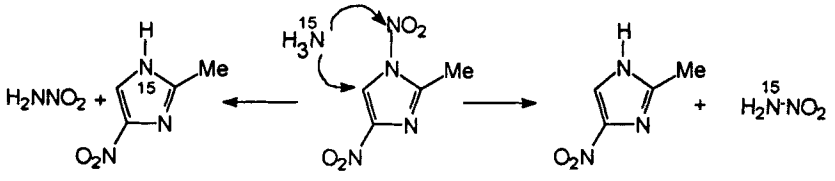
The preferable direction of the nucleophilic attack depends on the kind of substituent at the 1-position, the type of nucleophile and the character of the solvent used in the reaction. The attack of the nucleophile on the exocyclic center usually results in the removal of the substituent from the 1-position with the formation of 4(5)-nitroimidazole. The attack of the nucleophile on the carbon atom in the 5-position may result in *cine* substitution[11] or in the opening of the imidazole ring. Ring opening reactions are often observed in the reactions of 1,4-dinitroimidazoles with reagents containing a primary amino group[12,13]. When the reaction is carried out in water or in aqueous organic solvents, then, after ring opening, recyclization occurs, with the nitrogen atom from the 1-position of the initial compound being replaced with the nitrogen atom from the nucleophilic reagent:



The elimination of nitroamide results in the rearomatization of the imidazole ring. In the reaction solution, nitroamide is decomposed into nitrous oxide (N_2O) and water. We have suggested the present mechanism based on the analysis of the results of kinetic investigations[14], and the reaction with chiral amino reagents[15], and have finally confirmed it using an amine nucleophile labelled with ^{15}N in the primary amino group[16].

Analysing the above results, we made an assumption that it may be convenient to synthesise 2-methyl-4(5)-nitro[$^{15}N^{1(3)}$]imidazole using a method which consists of N-nitration of 2-methyl-4(5)-nitroimidazole to 2-methyl-1,4-dinitroimidazole and treating the latter with [^{15}N]ammonia

generated *in situ* from commercial [^{15}N]ammonium chloride[17] in aqueous solution of pH ≈ 8.5, with possible addition of organic co-solvent. In such conditions, the attack of ammonia on the 5-carbon atom of the imidazole ring should be preferable, and side-reactions such as alkaline hydrolysis of the substrate or *cine* substitution should be limited. To verify the above hypothesis, we collected a sample of gas liberated during the reaction, and, after introductory separation of the gas on a capillary chromatographic column, aimed at separating carbon dioxide which might possibly occur therein, we subjected it to MS analysis. We found that the MS spectrum contains intense ion peaks of m/e = 44 and 45, corresponding to molecular ions ^{15}NNO and N_2O. These results show that the ammonia attack on the 2-methyl-1,4-dinitroimidazole, takes place not only on the prefered 5-position of the imidazole ring but also on the nitrogen atom of the N-nitro group:



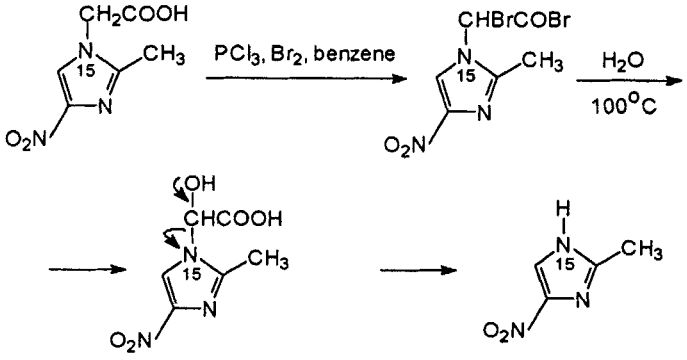
The above interpretation can be supported by the fact that the solid product obtained in this reaction is a mixture of labelled and unlabelled 2-methyl-4(5)-nitroimidazole in the ratio 3:2, as indicated by the shape of the mass spectrum (see the experimental). The ambident behaviour of 2-methyl-1,4-dinitroimidazole toward ammonia in aqueous medium was also supported by relevant quantum-chemical calculations[18].

Unlike the reaction of 2-methyl-1,4-dinitroimidazole with [^{15}N]ammonia leading to hardly separable mixture of the ^{15}N labelled and the unlabelled 2-methyl-4(5)-nitroimidazoles, the reaction of 2-methyl-1,4-dinitroimidazole with [^{15}N]labelled organic reagents containing primary amino group (assuming even parallel attack of the nucleophile on both electrophilic centers of the substrate) would result in the formation of 1-substituted 2-methyl-4-nitro[$^{15}N^{1}$]imidazole and possibly 2-methyl-4(5)-nitroimidazole which can be easily separated. However, the problem arises in the synthesis of 2-methyl-4(5)-nitro[$^{15}N^{1(3)}$]imidazole when the substituent from the 1-position of the labelled 4-nitroimidazole derivative is to be removed.

The literature offers only methods of N-dealkylation of imidazoles consisting in oxidation of e.g. reactive N-benzyl into benzoyl substituent easily removable when affected by water, or consisting in reductive removal of N-benzyl group e.g. by reaction with sodium amide in liquid ammonia[19]. As we have stated, under the conditions offered by the oxidation method, the generated 2-methyl-4(5)-nitroimidazole is subjected to further oxidation, and the application of the reductive method is hindered by the presence of a nitro group at the 4-position of the imidazole ring.

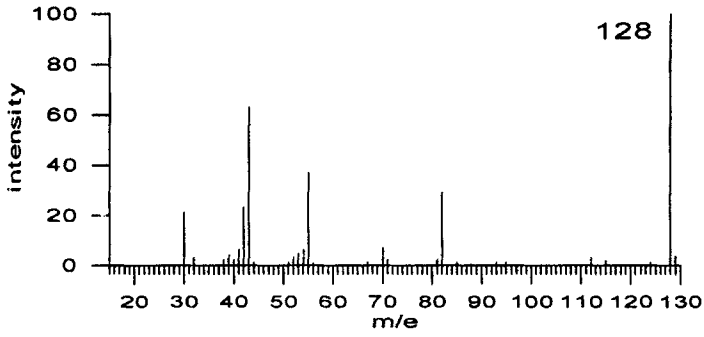
We have considered instead the possibility to N-debenzylate 1-benzyl-2-methyl-4-nitroimidazole by heating it in concentrated hydrobromic acid. However, yields of 2-methyl-4(5)-nitroimidazole after 24h of heating did not exceed 25%. Prolonging the heating time to 48h resulted in a decreased yield despite the still incomplete conversion of the initial compound. We have also tried to N-dealkylate (2-methyl-4-nitro-1-imidazol-1-yl)acetic acid under conditions of Schmidt degradation. We assumed that the possibly generated 1-aminomethyl-2-methyl-4-nitroimidazole, being a *gem*-diamino compound, will decompose in the course of reaction into the expected product and formaldehyde derivative. We have obtained, however, 2-methyl-4(5)-nitroimidazole, in quantity detectable only by means of TLC, despite applying considerable excess of hydrazoic acid generated *in situ* from sodium azide and sulfuric acid, or in the form of its chloroform solution.

It turned out that the effective way of N-dealkylation of 1-substituted 2-methyl-4-nitroimidazoles is the method based on the Wohlard-Zielinski reaction. As an initial compound, we reacted (2-methyl-4-nitro[$^{15}N^{1}$]imidazol-1-yl)acetic acid, easily obtained in the reaction of 2-methyl-1,4-dinitroimidazole with commercial [^{15}N]glycine[16]. We treated the compound with bromine and phosphorus trichloride in anhydrous benzene, and the crude reaction product, after the removal of volatiles from the post-reaction mixture, was subjected to hydrolysis. As a result, we obtained the expected 2-methyl-4(5)-nitro[$^{15}N^{1(3)}$]imidazole in ca. 40% yield.



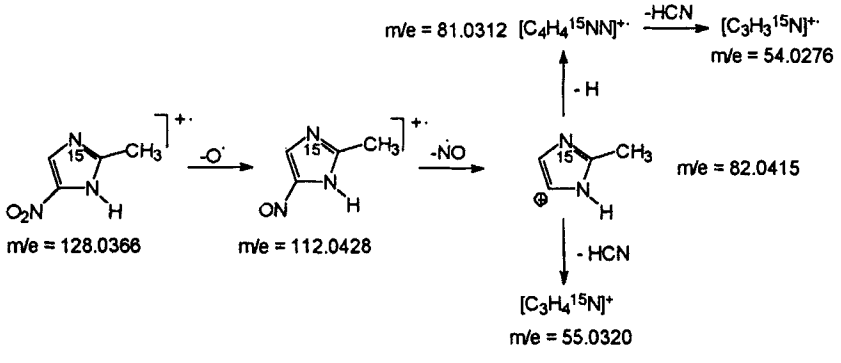
Further investigations aimed at increasing the yield were not carried out, but we believe that it is possible, provided the scale is increased. As indicated by the analyses, the product is homogeneous.

In the MS spectrum of the obtained product an intense molecular ion peak at m/e =128 can be observed, and ions of m/e: (M-16), (M-46) and (M-73) containing ^{15}N as well as the peaks of e.g. ion CH_3CO^+ of m/e = 43 and ion NO^+ of m/e = 30, which are present in the MS spectrum of unlabelled 2-methyl-4(5)-nitroimidazole, are also observed:



Based on the analysis of the HR-MS spectrum of the labelled product, and taking into consideration the fact that in the gaseous phase 2-methyl-4(5)-nitroimidazole exists as the 5-nitro tautomer[21], a number of fragmentations suggested in the literature may be authenticated; fragmentation by direct elimination of the CH_3CN from the molecular ion may be excluded due to the lack of ion (M-42) of m/e =86 in the spectrum.

The loss of an oxygen atom by the molecular radical cation (m/e =128.0366) results in the formation of a radical cation of m/e=112.0428 which, in turn, loses a nitrosyl radical, and hence, an imidazolium cation is formed (m/e=82.0415). This cation may lose hydrogen cyanide, which brings about the cation of m/e=55.0320, or loses the hydrogen atom (m/e=81.0312) and a HCN moiety (m/e=54.02276):



The obtained 2-methyl-4(5)-nitro[$^{15}N^{1(3)}$]imidazole may be used in the synthesis of 1-alkyl-4-nitro[$^{15}N^{1}$]imidazoles and 1-alkyl-5-nitro[$^{15}N^{3}$]imidazoles without additional purification, in accordance with known procedures[1,2,3,4]

EXPERIMENTAL

Melting points are uncorrected. Mass spectra of low resolution were taken with the GC-MS QP 2000 Shimadzu apparatus. Mass spectrum of high resolution was recorded on the Finnigan MAT 95 apparatus.

2-Methyl-1,4-dinitroimidazole (modification)[22]

Commercial 2-methyl-4(5)-nitroimidazole (10g) was suspended in glacial acetic acid ($60cm^3$), and, without cooling but with stirring, fuming nitric acid ($10cm^3$) and then acetic anhydride ($25cm^3$) were added portion-wise. After three hours of stirring, the mixture was poured into water and ice (325g : 75g). Immediately after the ice had melted, a white residue was filtered off, washed with cold water and dried to yield 10g (74%) of white crystalline and chromatographically homogeneous product of m.p. 120-121°C, which may be used in further syntheses without additional purification.

Reaction of 2-methyl-1,4-dinitroimidazole with [^{15}N]ammonia

To the water-dioxane solution at 25°C ($60cm^3$, 6 : 1 v/v) [^{15}N]ammonium chloride[17] (0.25g), 1M potassium hydroxide solution was added while stirring, until pH = 8.6. Then solid 2-methyl-1,4-dinitroimidazole (0.25g) was added. The acidifying of the solution proceeding as a result of the reaction was compensated by adding KOH solution while sustaining pH = 8.6 ± 0.2 for about 5 hours. Next, the post-reaction solution was acidified with concentrated hydrochloric acid until pH = 3 and the volatiles were evaporated under reduced pressure. The remaining part was washed with cold water (2 x $5cm^3$), dried and sublimed at 2mm Hg, at 200°C. The obtained product (30mg) was subjected to mass spectrometric analysis.
MS: 128(36), 127(21), 112(2), 111(1.3), 83(2.5), 82(20), 81(14), 80(2), 70(6), 55(38), 54(22), 53(10), 44(42), 43(100), 42(41), 41(11), 40(13), 30(8), 29(16), 28(34), 27(20).

Reaction of 2-methyl-1,4-dinitroimidazole with [^{15}N]glycine

The synthesis of (2-methyl-4-nitro[$^{15}N^1$]imidazol-1-yl)acetic acid, being the product of this reaction, was carried out according to the procedure described earlier[16]. The yield was 70%.

Dealkylation of (2-methyl-4-nitro[$^{15}N^1$]imidazol-1-yl)acetic acid

Phosphorus trichloride ($0.2cm^3$), bromine ($0.2cm^3$) and 4-nitroimidazole substrate (0.1g) were added to anhydrous benzene ($8cm^3$), and the solution refluxed for two hours in moisture-free conditions. Next, the volatiles were distilled off under reduced pressure. To the residue water ($5cm^3$) was added, and again the solution refluxed for 40 minutes. After the solution had been cooled to 25°C, it was neutralised with solid sodium hydroxide until pH was about 4. The precipitated residue was filtered off, washed with cold water and dried. The obtained product (30mg, 43%) was subjected to analysis without further purification.

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