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SYNTHESIS AND ^{15}N NMR SPECTRA OF 1- AND 4-^{15}N-2,3,5-TRIMETHYLPYRAZINES AND THEIR N-OXIDES[1)]

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SUMMARY

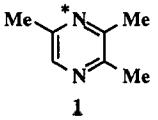
4-^{15}N-2,3,5-Trimethylpyrazine (**1**) was synthesized by dechlorination of 4-^{15}N-6-chloro-2,3,5-trimethylpyrazine (**5**), the key intermediate, derived from ^{15}N-DL-alanine (**3**).

1-^{15}N-2,3,5-Trimethylpyrazine (**2**) was prepared by decarboxylation of 1-^{15}N-2,3,5-trimethyl-pyrazine-6-carboxylic acid (**10**) obtained by the Pummerer type rearrangement of 1-^{15}N-tetramethylpyrazine 1-oxide (**7**) followed by oxidation.

1- And 4-oxides and 1,4-dioxides of the above ^{15}N-trimethylpyrazines were also obtained by treatment with sodium perborate in acetic acid.

^{15}N NMR spectra of the compounds thus prepared were measured and the assignment of two ^{15}N signals were certified.

Key Words: synthesis, 1-^{15}N-2,3,5-trimethylpyrazine, 4-^{15}N-2,3,5-trimethylpyrazine, N-oxides, ^{15}N NMR



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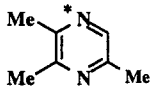

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INTRODUCTION

Pharmacological activity and natural occurrence of alkylpyrazines have caused increasing interest in the chemistry of these heterocylic compounds.[2] Some types of alkylpyrazines were known to show biological activity.[3] The effects of pyrazine ring N-oxidation on the ^{13}C NMR parameters of pyrazine and methylpyrazine derivatives have previously been studied by one of the present authors.[4]

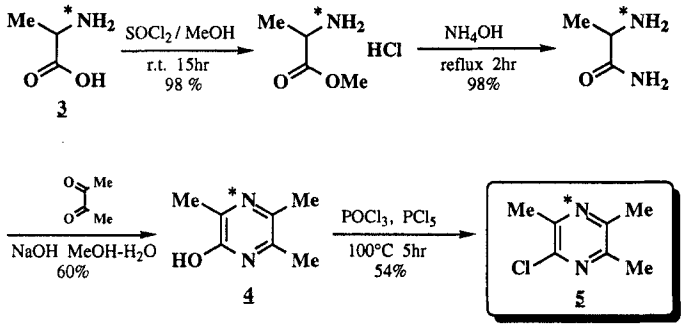
^{15}N NMR spectroscopy is also one of the best methods of presuming the chemical properties of each nitrogen atom of pyrazines. Although ^{15}N NMR studies on various pyrazine derivatives have been reported,[5] there is no comprehensive data on pyrazine, methylpyrazines and their mono- and dioxides.

During the ^{15}N NMR studies on unsymmetrically substituted pyrazine derivatives, we had to secure ^{15}N-enriched samples with 1- and 4-^{15}N-labelled compounds for definite assignment of two nitrogen signals. For this purpose, we tried to synthesize 1- and 4-^{15}N-2,3,5-tri-methylpyrazines as the target compounds.

RESULTS AND DISCUSSION

The present synthetic pathways are shown in Scheme 1. First of all, 4-^{15}N-6-hydroxy-2,3,5-trimethylpyrazine (**4**), the starting ^{15}N-labelled pyrazine in the present synthesis was prepared from **3** via ^{15}N-DL-alanine methyl ester and amide in 57% overall yield by known methods.[6,7] The key intermediate, 4-^{15}N-6-chloro-2,3,5-trimethypyrazine (**5**), was obtained from **4** by treatment with phosphoryl chloride and phosphorous pentachloride in 54% yield.[6]

4-^{15}N-2,3,5-Trimethylpyrazine (**1**; MS:M^+ m/Z 123), one of the present target compounds, was obtained from **5** in 63% yield



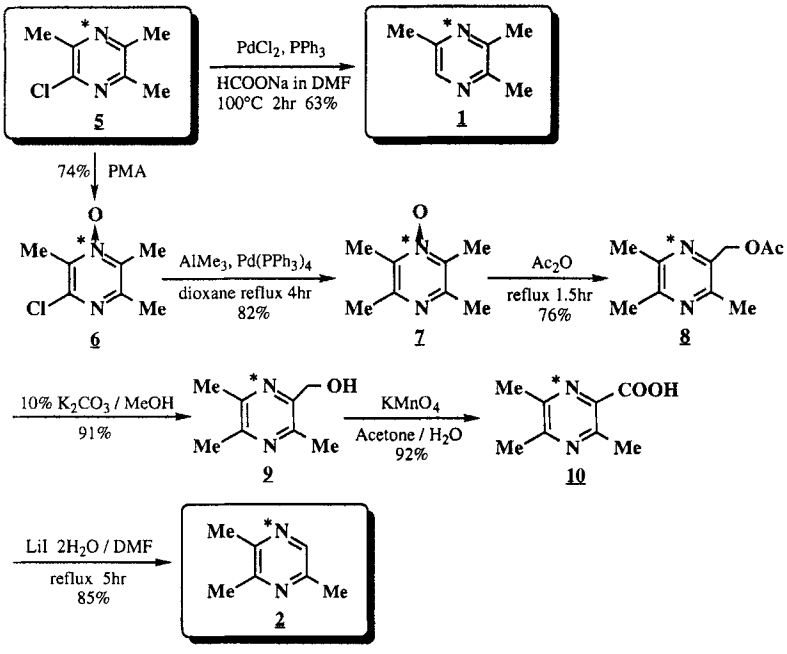
Scheme 1.

(isotopic yield: 3%) by dechlorination with palladium chloride, triphenyl phosphine and sodium formate in dimethylformamide at 100°C following the method described by Akita, et al..[8]

For the synthesis of another target, 1-^{15}N-2,3,5-trimethylpyrazine (**2**), we tried to make DL-alanine-^{15}N-amide, one of the other key intermediates for the 1-^{15}N counter part of **5**, by treating a commercial DL-alanine with ^{15}N-ammonia, however, the yield of ^{15}N-amide was unsatisfactorily low. Thus we had to come up with the following circuitous route from **5** to **2**. The key to this method was the Pummerer type rearangement of 1-^{15}N-2,3,5,6-tetramethylpyrazine 1-oxide (**7**).

Compound **5** was first oxidized with permaleic acid to give 4-^{15}N-6-chloro-2,3,5-trimethylpyrazine 4-oxide (**6**), as colorless crystals of mp 82-84°, in 74% yield. Compound **6** was then treated with trimethylaluminum and tetrakis-(triphenylphosphine)palladium in dioxane[9] to give **7** (MS:M^+ m/Z 153) in 82% yield.[9] By treating **7** with boiling acetic anhydride for 1.5 hrs, 1-^{15}N-6-acetoxymethyl-2,3,5-trimethylpyrazine (**8**; MS:M^+ m/Z 195) was obtained as a colorless liquid of bp 120-125°/3 mmHg in 76% yield.[10] This Pummerer type rearrangement of the 1-*O*-acetyl group in the intermediate formed from **7** is the key step to **2**.

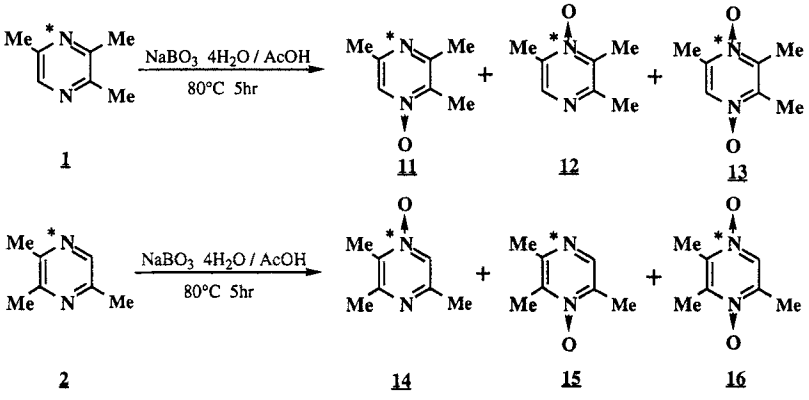
Hydrolysis of **8** was carried out by treatment with 10% potassium carbonate aqueous solution at room temperature giving 1-^{15}N-6-hydroxymethyl-2,3,5-trimethylpyrazine (**9**; MS:M$^+$ m/Z 153) which was then oxidized with potassium permanganate in aqueous acetone at room temperature giving 1-^{15}N-2,3,5-trimethyl-pyrazine-6-carboxylic acid (**10**) in good yield as colorless crystals, mp 111-112°. According to the method described by Taylor, et al.,[11] the acid **10** was decarboxylated by treatment with lithium iodide in refluxing dimethylformamide for 5 hrs to afford the objective product **2** (MS:M$^+$ m/Z 123) in 85% yield. The overall yield of **2** was 32% based on the intermediate **5**.



Scheme 2

Compound **1** was subjected to oxidation by heating with sodium perborate in acetic acid at 80° for 5 hrs[12] and the reaction mixture was separated by medium pressure column

chromatography using a silica gel column and a mixture of dichloromethane and hexane (2:1) as the eluent to give colorless crystals of 4-^{15}N-2,3,5-trimethylpyrazine 1-oxide (**11**; MS:M$^+$ m/Z 139), 4-^{15}N-2,3,5-trimethylpyrazine 4-oxide (**12**; MS:M$^+$ m/z 139), and 4-^{15}N-2,3,5-trimethylpyrazine 1,4-dioxide (**13**; MS:M$^+$ m/z 155) in 25%, 32%, and 15% yields, respectively. N-Oxidation of **2** was also carried out in a similar way to the above and the corresponding 1-oxide (**14**), 4-oxide (**15**) and 1,4-dioxide (**16**) were obtained in appreciable yields.(Scheme 3)



Scheme 3

^{15}N NMR spectra of the present ^{15}N-labelled trimethylpyrazine derivatives (**1**, **2**, **11**-**16**) were obtained by the INVGATE method and two characteristic signals for N-1 and N-4 were definitely assigned as shown in Figure 1. ^{15}N NMR spectra for compounds **12** and **15** are illustrated in Figure 2.

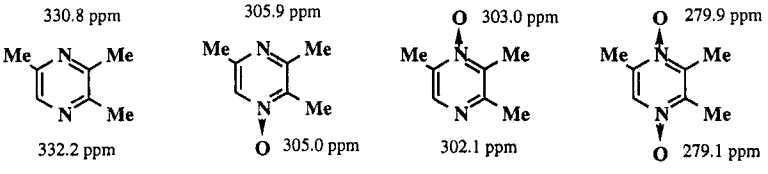


Fig. 1

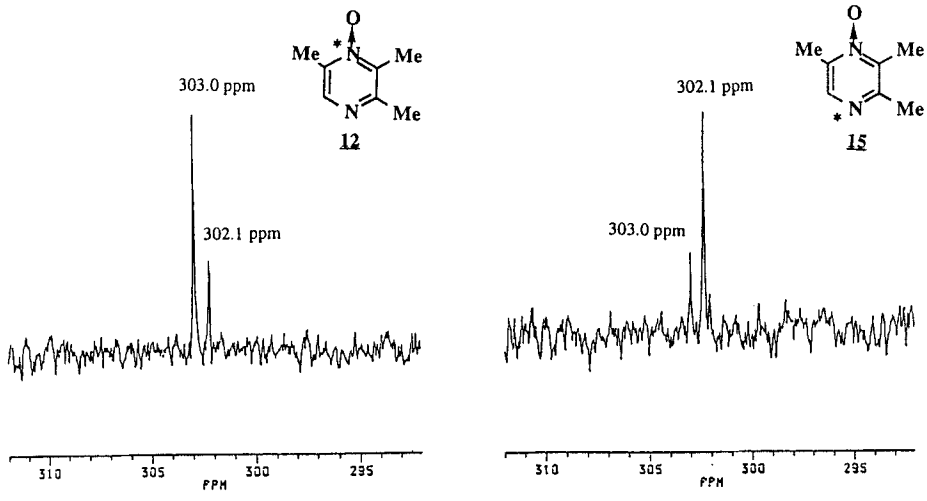


Fig. 2

EXPERIMANTAL

^{15}N-DL-Alanine (**3**) was purchased from ISOTEC Inc. (Miamisburg, Ohio, USA) and diluted with nine parts normal DL-alanine and used. The products and isotope yields were checked by mass spectra and the ratios of integrated peak areas in ^{15}N NMR.

The ^{15}N NMR spectra were obtained using a Bruker AM-500 NMR spectrometer (500 MHz) at 50.684 MHz. Measurement parameters are as follows: 32 K data points, 520 scanning, spectra width: 52 KHz, solvent: DMSO-d6, Temperature: 27°C. Chemical shifts are reported in ppm highfield from nitromethane (380 ppm) as the external standard.

Medium-pressure liquid chromatography was performed using a Kusano Kagaku KPW-14 apparatus equipped with a LiChrosorb SI-60 column (silica gel, 5 um, 4 x 250 mm stainless steel) and with an UVILOG-III UV photometer. All melting points are uncorrected.

4-^{15}N-6-Chloro-2,3,5-trimethylpyrazine 4-Oxide (6)

A mixture of 1.34 g (8.6 mmol) of 1-^{15}N-2,3,5-trimethyl-6-chloropyrazine (**5**), 0.98 g (17.2 mmol) of 60% hydrogen peroxide solution and 1.69 g (17.2 mmol) of maleic anhydride in 30 ml of chloroform was stirred overnight at room temperature. The

chloroform layer was washed with 10% potassium hydrogen carbonate solution and water to remove any acidic impurities and dried over unhydrous sodium sulfate. After evaporation of the solvent under reduced pressure, the residue was subjected to medium-pressure liquid chromatography and eluted by a mixture of hexane and ethyl acetate (8:2) to give colorless prisms (hexane) of **6** as colorless prisms of mp 82-84°C (1.1 g, 74%). Compound **5** was also revovered in 22% (0.30 g).

6:MS:m/z 173(M^+); ^1H NMR(300 MHz) δ ppm:2.58(s, 3H, CH_3), 2.63(s, 3H, CH_3), 2.93(s, 3H, CH_3); *Anal.* Calcd. for $C_7H_9N_2OCl$:C, 48.71; H, 5.25; N, 16.23. Found:C, 48.85; H, 5.25; N, 16.17.

1-^{15}N-2,3,5-Trimethylpyrazine-6-carboxylic acid (**10**)

A solution (40 ml) of 2-hydroxymethyl-3,5,6-trimethylpyrazine (**9**)(1.27 g,8.4 mmol) in 40 ml of acetone was added to a solution of potassium permanganate (2.1 g, 13.3 mmol) in 16 ml of water and the mixture was stirred overnight at room temperature. After removal of manganese dioxide by filtration, the filtrate was evaporated to remove acetone and the residual aqueous mixture was shaken with dichloromethane.

The aqueous layer was acidified with 10% hydrochloric acid and extracted with dichloromethane (30 ml x 2). The solution was dried over unhydrous sodium sulfate and concentrated under reduced pressure affording a pale yellow solid, which was recrystallized from hexane to give **10** as colorless prisms of mp 111-112° (1.28 g, 92%).

10:MS:m/z 166(M^+); ^1H NMR(300 MHz) δ ppm: 2.58(s, 3H, CH_3), 2.63 (s, 3H, CH_3), 2.93(s, 3H, CH_3); *Anal.* Calcd.for $C_8H_{10}N_2O_2$: C,57.82; H,6.07; N,16.86. Found: C,57.80; H,5.96; N, 16.87.

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