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Research Article

Synthesis and mass spectra of labelled 4(5)-nitro-1H-imidazole-5(4)-carbonitriles

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Summary

Cine nucleophilic substitution of 1,4-dinitroimidazole and its 2-methyl derivative with nitrogen-15 or carbon-13 potassium cyanides afforded, respectively, labelled 4(5)-nitro-1H-imidazole-5(4)-carbonitriles. Detailed mass spectra analysis led to the conclusion that during fragmentation in mass spectrometer the labelled atoms are present in all the main fragmentation ions of m/z higher than 42. Copyright © 2002 John Wiley & Sons, Ltd.

Key Words: synthesis; nitroimidazolecarbonitrile; mass spectrometry

1. Introduction

Recently, we have published the efficient synthesis of hitherto unknown 4(5)-nitro-1H-imidazole-5(4)-carbonitriles, convenient starting materials for syntheses of 7 or 9 substituted purine derivatives.[1] The synthesis involves reaction of 1,4-dinitroimidazoles with potassium cyanide in aqueous methanol in the presence of sodium bicarbonate at room temperature. Moderate to high yields of the products and simplicity of the method encouraged us to synthesize compounds labelled in the

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cyano group. This work, together with synthesis of 4-nitroimidazoles with nitrogen-15 as one of the ring atoms also published by us[2] and with well-known methods of 4(5)-nitro-5(4)-imidazolecarbonitriles conversion to purines, gives a simple route to synthesis of nucleobases labelled in either imidazole or pyrimidine or both rings.

Results and discussion

Four 4(5)-nitro-1H-imidazole-5(4)-carbonitriles labelled in the cyano group were obtained in practically pure states in yields over 50%. Considering the small scale of the syntheses the yields are satisfactory. In standard mass spectra, recorded at 70 eV for compounds ^{13}C- and ^{15}N-labelled in the cyano group, molecular peaks and almost all fragmentation peaks of m/z higher than 37 corresponded to similar, but 1 unit smaller, peaks in the mass spectra recorded for non-labelled compounds. The only exceptions were peaks of $m/z = 69$ present in the spectra of all 4(5)-nitro-5(4)-imidazolecarbonitriles and peaks of $m/z = 83$ or 42 (CH_3CNH^+) present in the spectra of all 2-methyl-4(5)-nitro-5(4)-imidazolecarbonitriles (Tables 1 and 2). Most of the peaks observed in the spectra of both groups of 4(5)-nitro-5(4)-imidazolecarbonitriles are typical for spectra of 4- and 5-nitroimidazoles. This observation concerns peaks of m/z: M+, M-16, M-30, M-46 and M-73. The appearance of peaks of m/z = M-114 and M-87 in the spectra of 2-methyl-4(5)-nitro-5(4)-imidazolecarbonitriles corresponding to peaks of m/z = M-100 and M-73 in the spectra of 4(5)-nitro-5(4)-imidazolecarbonitriles can be easily explained considering other data concerning behaviour of nitroimidazoles in mass spectrometer[3–5] and a reasonable assumption (confirmed by us by semi-empirical AM1 and PM3 calculations) that in the gas phase a fast equilibrium exists between 4-nitroimidazole-5-carbonitriles and 5-nitroimidazole-4-carbonitriles.

From high-resolution mass spectra exact values of m/z for the most intensive peaks were found. They are collected in Tables 3 and 4. These data confirm the fragmentation routes assumed earlier. The ions of m/z 53 in the spectra of non-labelled or of m/z 54 in the spectra of labelled compounds are daughter ions of the ions of $m/z = 79$, 80 or 81. The latter ions are daughters of (M-NO) or ($M-NO_2$) ions forming from M^+ for 4(5)-nitro-5(4)-imidazolecarbonitriles and their 2-methyl derivatives, respectively.

Table 1. Ions present in EI mass spectra (70 eV) of 4(5)-nitro-5(4)-imidazolecarbonitriles

Compd.	Ions: m/z (relative intensity %)								
	M^+	M-16$^+$ (M-O)	M-30$^+$ (M-NO)	M-46$^+$ (M-NO_2)	M-58$^+$ (?)	$C_2HN_2O^+$ (?)	M-73$^+$ (M-NO_2-HCN)	M-85$^+$ (?)	M-100$^+$ (M-NO_2-HCN-HCN)
Non-labelled	138 (100)	122 (8)	108 (12)	92 (25)	80 (1)	69 (8)	65 (44)	53 (30)	38 (24)
^{13}C-labelled	139 (100)	123 (8)	109 (10)	93 (28)	81 (<1)	69 (15)	66 (52)	54 (32)	39 (28)
^{15}N- labelled	139 (100)	123 (6)	109 (10)	93 (34)	81 (<1)	69 (18)	66 (56)	54 (40)	39 (28)

Table 2. Ions present in EI mass spectra (70 eV) of 2-methyl-4(5)-nitro-5(4)- imidazolecarbonitriles

Compd.	Ions: m/z (relative intensity %)									
	M^+	M-16$^+$ (M-O)	M-30$^+$ (M-NO)	M-46$^+$ (M-NO_2)	M-73$^+$ (M-NO_2-HCN)	$MeC_2N_2O^+$ (?)	M-87$^+$ (M-NO_2-MeCN)	M-99$^+$ (?)	MeCN$^+$	M-114$^+$ (M-NO_2-MeCN-HCN)
Non-labelled	152 (100)	136 (4)	122 (2)	106 (100)	79 (42)	83 (<1)	65 (20)	53 (30)	42 (92)	38 (12)
^{13}C-labelled	153 (100)	137 (4)	123 (2)	107 (84)	80 (36)	83 (<1)	66 (16)	54 (20)	42 (80)	39 (8)
^{15}N-labelled	153 (100)	137 (6)	123 (1)	107 (84)	80 (36)	83 (<1)	66 (16)	54 (20)	42 (80)	39 (8)

Table 3. Comparison of high-resolution MS spectra of 4(5)-nitro-1H-imidazole-5(4)- carbonitriles non-labelled and ^{13}C- or ^{15}N-labelled in the cyano group

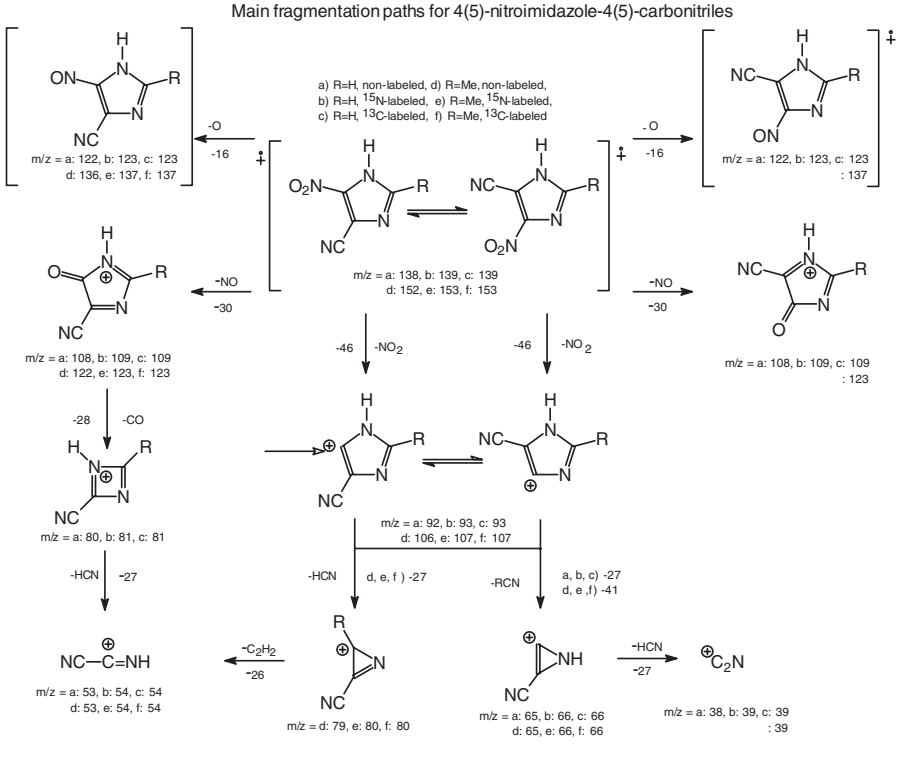
Ion	M^+	M-O, M-NO	M-NO-CO	M-NO_2	M-NO_2-HCN	M-NO-HCN-HCN	M-NO_2-HCN-HCN
Compound				*m/z* (%); structure			
Non-labelled	138.01790 $C_4H_2O_2N_4$	122, 108	80	92.02488 $C_4H_2N_3$	65.01417 C_3HN_2	53.01373 C_2HN_2	38
^{13}C-labelled	139.02144 $C_3^{13}CH_2O_2N_4$	123, 109	81	93.02836 $C_3^{13}CH_2N_3$	66.01701 $C_2^{13}CHN_2$	54.01738 $C^{13}CHN_2$	39
^{15}N-labelled	139.01507 $C_4H_2O_2^{15}NN_3$	123, 109	81	93.02187 $C_4H_2^{15}NN_2$	66.01126 $C_3H^{15}NN$	54.01127 $C_2H^{15}NN$	39

Table 4. Comparison of high-resolution MS spectra of 2-methyl-4(5)-nitro-1H-imidazole- 5(4)-carbonitriles non-labelled and ^{13}C- or ^{15}N-labelled in the cyano group

Ion	M^+	M-O, M-NO	M-NO_2	M-NO_2-HCN	M-NO_2-MeCN	M-NO_2-HCN-C_2H_2	M-NO_2-MeCN-HCN
Compound				*m/z* (%); structure			
Non-labelled	152.03368 $C_5H_4O_2N_4$	136, 122	106.04073 $C_5H_4N_3$	79.02952 $C_4H_3N_2$	65.01397 C_3HN_2	53.01404 C_2HN_2	38
^{13}C-labelled	153.0371 $C_4^{13}CH_4O_2N_4$	137, 123	107.04407 $C_4^{13}CH_4N_3$	80.03343 $C_3^{13}CH_3N_2$	66.01745 $C_2^{13}CHN_2$	54.017248 $C^{13}CHN_2$	39
^{15}N-labelled	153.03028 $C_5H_4O_2^{15}NN_3$	137, 123	107.03735 $C_5H_4^{15}NN_2$	80.02667 $C_4H_3^{15}NN$	66.01109 $C_3H^{15}NN$	54.01112 $C_2H^{15}NN$	39

The ions of m/z 54 forming from the labelled compounds still contain labelled atoms. Thus, they arise by elimination of unlabelled hydrogen cyanide or acetylene, respectively, as it is shown in the Scheme. This is the main difference in fragmentations of nitroimidazolecarbonitriles without and with methyl group in the position 2. The formation of ions of $m/z = 69$ for 4(5)-nitro-5(4)-imidazolecarbonitriles, and of ions of $m/z = 83$ for 2-methyl derivatives, respectively, is not known. The ions are present in the non-labelled and labelled compounds, indicating that apparently they arise as the results of intermediate radical cations of 4(5)-nitroso-5(4)-imidazolecarbonitriles or 2-methyl-4(5)-nitroso-5(4)-imidazolecarbonitriles decomposition with departures of radicals containing the cyano groups. The possible structures of the ions could be $C_2HN_2O^+$ ($m/z = 69$) and $MeCN_2O^+$ ($m/z = 83$), respectively. Unfortunately, the exact masses of these ions have not been found.

The most probable fragmentation paths of the studied compounds are shown in Scheme 1.



Scheme 1. Main fragmentation paths for 4(5)-nitroimidazole-4(5)-carbonitriles.

It is rather surprising that the very common fragmentation of nitroimidazoles in mass spectrometry involving formation of M-O ion and its further fragmentation does not play any important role in fragmentation of the studied 4(5)-nitro-1H-imidazole-5(4)-carbonitriles.

Experimental

Synthesis of labelled compounds

1,4-Dinitroimidazole (217 mg, 1.37 mmol) or 2-methyl-1,4-dinitroimidazole (236 mg, 1.37 mmol) was added while stirring at 25°C to aqueous methanol (1:1 v/v, 5 ml) followed by addition of labelled ^{15}N or ^{13}C potassium cyanide (100 mg, 1.51 mmol) and of sodium bicarbonate (115 mg, 1.37 mmol). Stirring was continued for 10 min and the mixture was left overnight in darkness at room temperature. The resulting post-reaction mixture was acidified with concentrated hydrochloric acid, the solvents were evaporated; the solid residue was rinsed in water (5 ml) and dried under diminished pressure. In this way, the following compounds were obtained:

4(5)-Nitro-1H-imidazole-5(4)-^{13}carbonitrile: 104 mg (54.6%),
4(5)-Nitro-1H-imidazole-5(4)-carbo^{15}nitrile: 101 mg (53%),
2-methyl-4(5)-nitro-1H-imidazole-5(4)-^{13}carbonitrile: 127 mg (60.6%),
2-methyl-4(5)-nitro-1H-imidazole-5(4)-carbo^{15}nitrile: 123 mg (58.7%).

Spectroscopic properties and melting points like those reported for non-labelled compounds.[1]

Mass spectrometry

EI mass spectra of all the compounds were obtained with an Finnigan MAT 95 spectrometer operated under the following conditions: electron energy 70 eV, electron beam current 0.7 mA, accelerating voltage 4.8 kV, ion source temperature 250°C. Resolution during measurements was at least 10 000 with the internal reference PFK standard. Samples were introduced by means of direct inlet system.

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