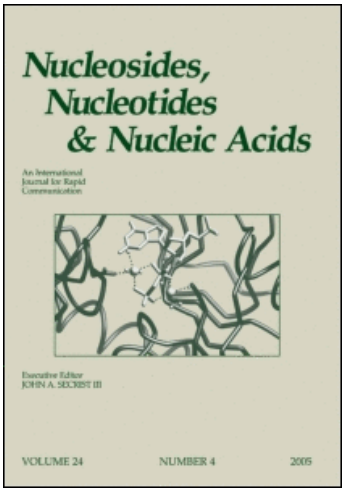

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An Unusual Iodine Monochloride Chlorination of an Imidazole Nucleoside

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AN UNUSUAL IODINE MONOCHLORIDE CHLORINATION OF AN IMIDAZOLE NUCLEOSIDE

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Abstract. The reaction of iodine monochloride with the imidazole nucleoside, 5-amino-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide, provides the 2-chloroimidazole nucleoside in good yield.

INTRODUCTION

Iodine monochloride (ICl) is an iodinating agent[1] commonly employed for effecting the electrophilic iodination of aromatic moieties of amino acids such as tyrosine and histidine residues of proteins[2-5] and of other biological substrates including nucleosides.[6] However, the possibility of concurrent chlorination when employing this agent has not been investigated. In this study we describe an attempted ICl[7] iodination of 5-amino-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide[8] (1) in anhydrous tetrahydrofuran at -5°C and formation of the unexpected chlorinated product, 5-amino-2-chloro-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (4). The product 4 was isolated by silica gel column chromatography, and the structure determined by ^{1}H NMR and mass spectrometry. The original signal for the proton at the position-2 of (1) is absent indicating that position-2 is the site of halogenation. The mass spectrum of 4 exhibits molecular ion peaks at m/z = 418 (^{35}Cl) and m/z = 420 (^{37}Cl) for the chloro compound (Figure 1). Further proof for structure of 4 was evident from its mp: 188-189°C (lit.[9] mp: 189-190°C) which was not depressed when upon mixing 4 with an authentic sample.[9] In addition, its TLC mobility and UV spectrum properties were identical to those of the authentic sample prepared by a procedure described in the literature.[9]

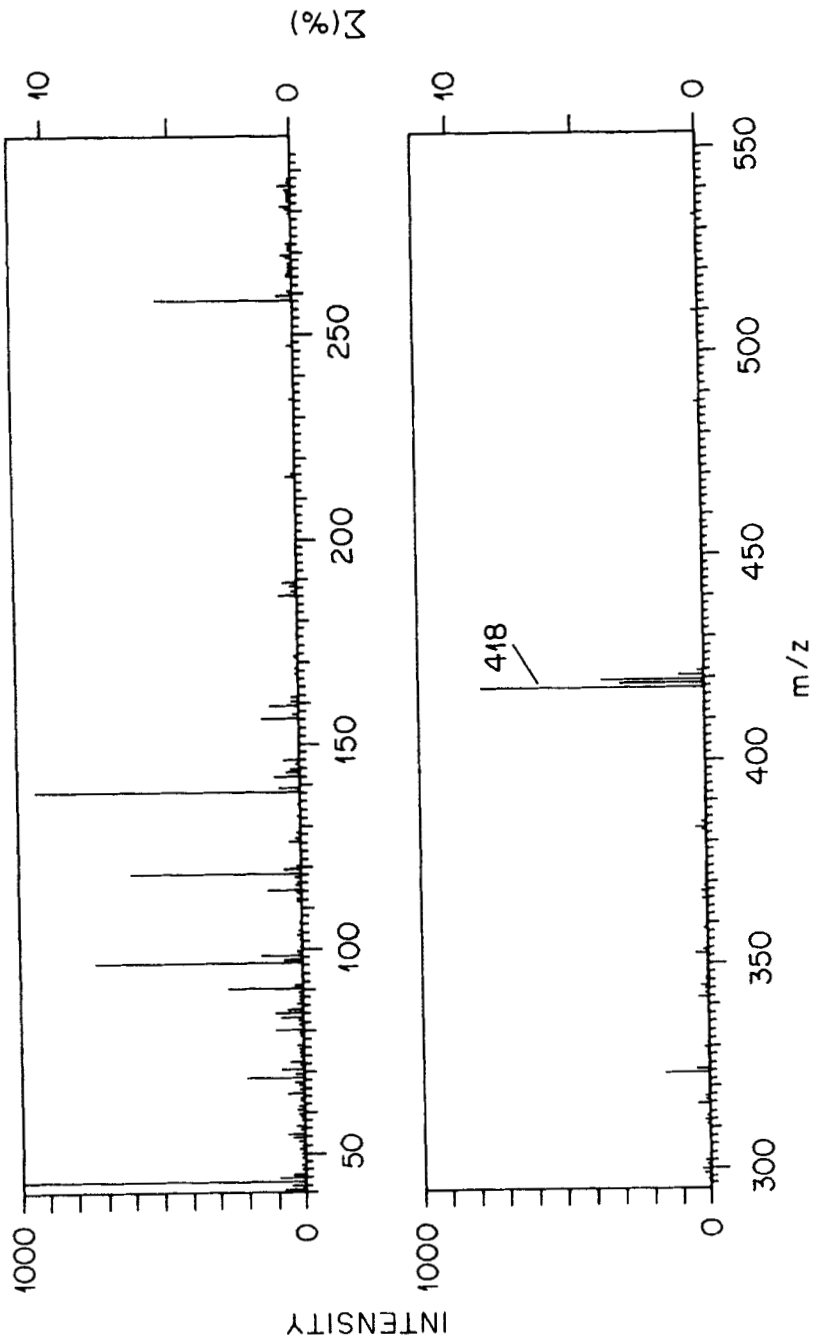
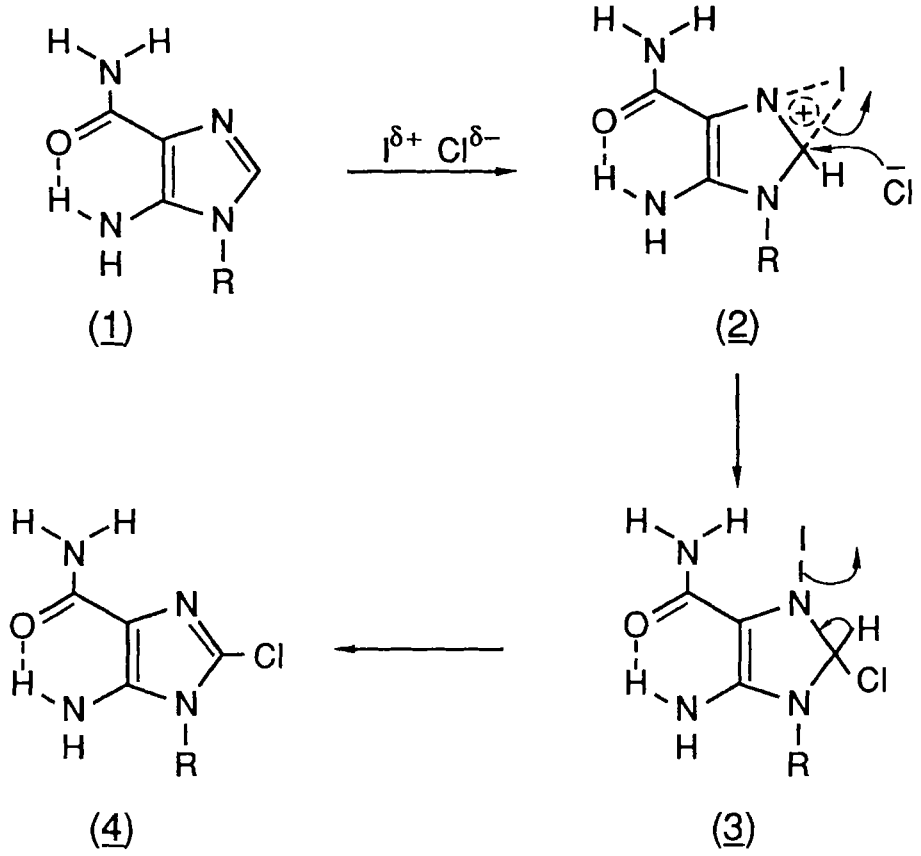


FIGURE 1. Electron ionization mass spectrum of 4 (m/z = 418).



SCHEME I

RESULTS AND DISCUSSION

A possible mechanism for the formation of the observed chlorination product is outlined in Scheme I based on a polarized iodine-chlorine bond with a partial positive charge on the iodine in ICl. The hydrogen bonded structure of nucleoside 1 would be a favorable substrate for ICl addition on the C^2,N^3-double bond resulting in intermediate formation of the iodonium ion 2. Subsequent nucleophilic attack of chloride on 2 would provide intermediate 3 which could undergo aromatization via elimination of HI to yield the 2-chloro product 4.

Although the synthesis of 4 using N-chlorosuccinimide (NCS) has been described in the literature,[9] the nature of ICl chlorination of 1 to yield 4 is unique and requires relatively mild conditions. Other nucleoside chlorination methods reported in the literature include use of *p*-toluenesulfonyl chloride,[10] iodobenzene dichloride,[6] HCl- and *m*-chloroperbenzoic acid in an aprotic solvent,[11] *tert*-butyl hypochlorite,[12] tetrabutylammonium iodotetrachloride,[13] NCS-acetic acid[14] and Cl_2-H_2O under photolytic conditions.[15] In view of these few chlorination procedures of nucleosides available, we further investigated the scope of ICl for chlorination of nucleosides. A variety of nucleosides including 2',3'-O-isopropylideneadenosine, 2',3',5'-tri-O-acetylguanosine and 2-nitro-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)imidazole[16] were treated with ICl in THF. In each case the nucleoside substrate was recovered unchanged and no significant chlorination was observed. These results indicate that ICl chlorination of 1 described here may be an unusual case. However, care should be exercised during ICl iodinations of biological substrates to account for potential formation of chlorinated byproducts.

EXPERIMENTAL

Analytical grade solvents and reagents were used. Proton nuclear magnetic resonance spectra (^{1}H NMR) were determined on a Hitachi Perkin-Elmer Model R-20A spectrometer using DSS as an internal standard. Melting points (mp) were obtained on a Thomas Hoover apparatus and are uncorrected. Baker analyzed silica gel powder (60-200 mesh) was used for column chromatography. The homogeneity of the compounds was checked by thin-layer chromatography using precoated (250 μ) ICN (Life Science Group) Woelm TLC plates (silica gel F-254). Short-wave ultraviolet light (mineralight UVS 11) was used to detect the spots.

5-Amino-2-chloro-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (4).

A solution of 1 (384 mg, 1 mmol) and ICl (163 mg, 1 mmol) in anhydrous THF (6 mL) was stirred at -5°C for 3 h. The solvent was evaporated under vacuum and the residue was passed through a column of silica gel packed in chloroform. Elution of the column with chloroform followed by chloroform-ethyl acetate (1:1, v/v) provided 4 which was crystallized from water. Yield: 250 mg (60%), mp: 188-189°C (lit.[9] mp: 189-190°C). ^{1}H NMR data (Me_2SO-d_6), δ 6.92 (s,

2, $CONH_2$), 6.10 (s, 2, NH_2), 5.90 (d, 1, $J_{1',2'}$ = 6 HZ, H-1'), 4.36 (br s, 3, H-4', H-5') were in agreement with that reported previously.[9] The mass spectral data (m/z: 418 for $C_{15}H_{19}N_4O_8Cl$) are reported in Figure 1.

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