Studies on the Selective S-oxidation of Albendazole, Fenbendazole, Triclabendazole, and Other Benzimidazole Sulfides

Olivia Soria-Arteche, Rafael Castillo, Alicia Hernández-Campos, Marcela Hurtado-de la Peña, Gabriel Navarrete-Vázquez, José Luis Medina-Franco, Kathia Gómez-Flores

1 Departamento Sistemas Biológicos, DCBS. Universidad Autónoma Metropolitana-Xochimilco, México, D.F. 04960, México. Email: soriao@correo.xoc.uam.mx
2 Departamento de Farmacia, Facultad de Química, Universidad Nacional Autónoma de México, México D.F. 04510, México
3 Facultad de Farmacia, Universidad Autónoma del Estado de Morelos, Cuernavaca, Morelos 62210, México

Recibido el 16 de agosto de 2005; aceptado el 14 de diciembre de 2005

Abstract. The selective S-oxidation of albendazole, fenbendazole, and other benzimidazole sulfides with sodium periodate in acid medium, afforded the corresponding sulfoxides or sulfones. In contrast, triclabendazole and other 2-methylthiobenzimidazole derivatives could not be S-oxidized under the same smooth conditions with this reagent, but with MCPBA, a stronger oxidizing agent.

Keywords: Albendazole, fenbendazole, triclabendazole, metabolites, S-oxidation.

Introduction

A large group of wide spectrum, high efficiency anthelmintics, such as the benzimidazole 2-carbamates (BZC), is marketed worldwide for the control of helminthiasis. It has been reported that benzimidazole anthelmintics with a sulfide group are the most active against intestinal nematodes in humans, as well as in animals [1-3]. Included among these anthelmintics are albendazole 1, fenbendazole 2 and triclabendazole 3 (Figure 1).

Benzimidazole sulfides 1, 2, and 3 undergo first pass biotransformation in the organism, where the sulphur atom is oxidized to produce the active antiparasitic sulfoxides 4 [1,4-5], 6 [6-7], and 8 [8-9], respectively. Further oxidation produces the inactive sulfones 5, 7 or 9.

Metabolites 4, 5 and 7 are commercially available but not easily affordable. Not so for 6, which is easily available at a relatively low price. Although there are reports in the pertinent literature for the synthesis of 4, 5[1,10-12]; 6, 7 [2]; and 8, 9 [13], in addition to the general methods of S-oxidation [13], these are not easy to carry out, or fail, due to insolubility problems in 1-3, which often leads to mixtures of sulfoxides and sulfones that are difficult to separate. The need of these metabolites in helminthiasis chemotherapy research [2,3,5] makes the development of new preparation methods highly desirable, in particular, those that employ common reagents, mild reaction conditions and convenient working procedures.

In this paper we present an efficient, high yield method for the selective S-oxidation of 1, 2 and 3 to obtain 4, 6 and 8, as well as the selective S-oxidation of other benzimidazole sulfides 10, 12 and 17 to obtain 11, 13 and 18, respectively (cf. Figures 2 and Scheme). In these studies, sodium periodate in acid medium was used as the oxidizing agent. This reagent does not over-oxidize 1 under low temperature conditions [15-17]. In addition, aqueous mixtures of acetic acid-acetonitrile were used as solvent, which allowed carrying out the reactions at different temperature conditions for better control, thus avoiding over oxidation.

Results and Discussion

The results of the oxidation reactions of 1-3, 10, 12 and 17 are shown in Table 1.
Oxidation of 1 with sodium periodate in acetic acid to obtain albendazole sulfoxide 4 was studied under several temperature conditions. At -10°C it was necessary to add acetonitrile as co-solvent to avoid precipitation of 1 and to complete its oxidation; however, the reaction was incomplete. On the other hand, at 25°C, a mixture of 1, 4 and 5 was produced. The best results were obtained when the reaction was carried out in acetic acid-water at 0-5°C, in this case, 4 was obtained as the only product in a 97% yield. Its 1H NMR spectrum showed a multiplet at 2.72-2.86 ppm, characteristic of the diastereotopic α-methylene hydrogens next to the chiral sulfoxide. The mass spectrum showed a peak at m/z 281, which is in agreement with the molecular ion of 4. The purity of 4 was confirmed by HPLC. Only one peak with a 6.75 min retention time was observed.

When 1 was oxidized with excess of sodium periodate at 25°C for longer periods of time, sulfone 5 was the only product obtained in a 90% yield. The 1H NMR spectrum now showed a triplet at 3.21 ppm for the nondiastereotopic α-methylene hydrogens next to the sulfone group. The mass spectrum showed the molecular ion peak of 5 at m/z 297. The purity was confirmed by HPLC, a single peak with a 5.21 min retention time was observed.

Encouraged by these results, we decided to test the periodate oxidation method with compounds 2, 3 and other benzimidazole sulfides, 10 and 12, which are currently being studied as experimental new antiparasitic agents (Figure 2).

Oxidation of 2 at 15°C gave sulfoxide 6 in a 95% yield. Its structure was confirmed by mass spectrometry. When the temperature and the equivalents were increased (60°C, 2.8 eq.), sulfone 7 was obtained as the only product in a 67% yield.

In order to increase the solubility of 3 and prevent its precipitation, the oxidation reaction with sodium periodate was undertaken with acetonitrile as co-solvent; however, although a solution was attained, no change in 3 was observed, even at 20°C. In this case, we had to use m-chloroperbenzoic acid (MCPBA), a stronger oxidizing agent, and obtained 8 at 0-5°C [18].

In the case of compound 10, the oxidation with sodium periodate in acetic acid-acetonitrile proceeded smoothly at 0-5°C to afford sulfoxide 11 in a 90% yield. The oxidation of 12 to the sulfoxide 13 also failed with sodium periodate, but it was easily achieved with MCPBA. The lower reactivity of sulfides such as 3 and 12 can be attributed to a reduced electron density on sulfur because of the inductive effect of the imidazole ring nitrogen atoms. This contention is supported by the regiospecific and high yielding oxidation of the bis-sulfide 17 (Scheme 1[19, 20]; see Experimental section for details of synthesis) to the monosulfoxide 18, and by electron density calculations (Fig. 3).

**Conclusions**

A practical, mild and efficient method for the S-oxidation of albendazole 1, fenbendazole 2, and benzimidazole sulfide 10 was developed. The method consists in treating a cold solu-
tion of these compounds with sodium periodate to generate the corresponding sulfoxides. The related sulfones were obtained at higher temperatures. In the case of 2-(methylthio)benzimida-
dazoles, such as triclabendazole, the S-oxidation was achieved with MCPBA, a stronger oxidizing agent.

Experimental

Melting points were determined on a Büchi B-540 melting point apparatus and are uncorrected. Reactions were monitored by TLC on 0.2 mm precoated silica gel 60 F254 plates (E. Merck). Infra-red spectra were recorded in a Perkin-Elmer FT-IR-1600 spectrometer on KBr pellets, the absorption bands are given cm⁻¹. MS were recorded on a JEOL JMS-SX102A spectrometer by electron impact (EI) of low and high resolution (HR-MS), and FAB. ¹H NMR spectra were measured with a Varian model EM-390 (300 MHz) spectrometer. Chemical shifts are given in ppm relative to Me₄Si (δ = 0) used as internal standard. The solvent employed was DMSO-d₆, except for 11 and 17 that was CDCl₃. J values are given in Hz. The following abbreviations are used: s, singlet; d, doublet; t, triplet; sext, sextuplet; m, multiplet; bs, broad signal. HPLC analyses were performed in a Perkin Elmer serie 200LC, UV 785A detector: column C-8, mobile phase: CH₃OH-H₂O-CH₃CN-CH₃COOH (40:40:19.4:0.6). Starting materials 1, 2, and 3 were obtained commercially, whereas 10, 12, and 14 were synthesized in our laboratories.

General method for the synthesis of propylsulfinyl derivatives (4, 6, 11 and 18) and propylsulfonyl derivatives (5, 7). Into a stirred solution of 1, 2, 10, or 17 in AcOH or AcOH/CH₃CN (1:1) was slowly added, dropwise, a solution of NaIO₄ in a mixture of H₂O/AcOH. The mixture was stirred, then, the solvent removed in vacuo without heating. The progress of the reaction was monitored by TLC. The residue was suspended in brine and neutralized with a saturated solution of potassium carbonate, the resulting suspension was filtered, and the residue washed with water and air dried.

Methyl 5-[(propylsulfinyl)-1H-benzimidazol-2-yl]carbamate (4). Following the general procedure, 1 (0.5 g, 1.89 mmol) in 6.5 mL AcOH and NaIO₄ (0.403 g, 1.89 mmol) in 14 mL of H₂O/AcOH (5:2) were stirred at 0-5°C for 2 h and gave 4.
Methyl [5-(propylsulfonyl)-1H-benzimidazol-2-yl]carbamate (5). Following the general procedure, 1 (1.0 g, 3.76 mmol) in 15 mL of AcOH and NaIO4 (2.015 g, 9.42 mmol, 2.5 eq.) in 25 mL of H2O/AcOH (4:1) were stirred at 15°C for 2 h and gave 11 (1.01 g, 90%) as a white powder. Mp: 226-227°C. IR νmax 3352 (NH), 1731 (C=O), 1276 and 1131. MS (EI) (m/z): 297 (M+). H-RMS (EI) calcd for C12H15N3O3S (M+) 297.0783. Found: 297.0792. 1HNMR: δ 0.89 (3H, t, J= 7.5, CH3CH2CH2SO2), 1.55 (2H, sext, 7.5, CH2CH2SO2), 2.32 (2H, t, J= 7.5, CH2SO2), 3.80 (3H, s, CH3O), 7.58 (1H, dd, J = 8.2; J = 1.5, H-6), 7.62 (1H, d, J = 8.2, H-7), 7.91 (1H, s, H-4); and 12.06 (bs, NH, int. D2O). HPLC: rt: 5.21 min.

Methyl [5-(phenylsulfonyl)-1H-benzimidazol-2-yl]carbamate (6). Following the general procedure, 2 (0.5 g, 1.67 mmol) in 13 mL of AcOH/CH3CN and NaIO4 (0.393 g, 1.84 mmol) in 6 mL of H2O/AcOH (5:2) were stirred at 15°C for 2 h and gave 6 (0.527 g, 95%) as a white powder, after recrystallization from AcOEt-Et2O. Mp: 253.9°C. TLC (Toluene-THF-AcOH, 5:1:1). IR νmax 3392 (NH) and 1083 (S=O). MS (EI) (m/z): 254 (M+). HRMS (EI) calcd for C14H10Cl2N2O3S (M+) 254.0548. Found: 254.0560. 1HNMR: δ 0.99 (3H, t, J= 7.34, CH3CH2CH2SO2), 1.47-1.79 (2H, m, CH2CH2SO2), 2.75 (3H, s, CH3S), 2.68-2.87 (2H, m, CH3SO2), 7.38 (1H, dd, J= 8.4, J= 1.5, H-6), 7.58 (1H, dd, J = 8.4, J = 0.6, H-7), and 7.69 (1H, dd, J = 1.5, J = 0.6, H-4), and 13.2 (bs, NH, int. D2O).

5-Chloro-6-(2,3-dichlorophenoxy)-2-(methylsulfinyl)-1H-benzimidazole (8). To a stirred solution of 3 (0.50 g, 1.37 mmol) in 50 mL of CHCl3 was slowly added, dropwise, a solution of MCPBA (0.338g, 1.37 mmol) in 4 mL of CHCl3 at 0-5°C. The progress of the reaction was monitored by TLC (CHCl3-MeOH, 95:5.0:5). At the end of the reaction the solvent was removed in vacuo without heating, the residue was suspended in brine and neutralized with a saturated solution of potassium carbonate. The mixture was extracted with CHCl3 (3x20 mL). The combined organic extracts were dried with anhydrous sodium sulphate, filtered and evaporated in vacuo to give 8 (0.389 g, 75%) of a white soapy powder. Mp: 176-178°C. IR νmax: 3168 (NH), 1050 (SO). MS (EI) (m/z): 376 (M+). HRMS (EI) calcd for C14H10Cl2N2O3S (M+) 375.9450. Found: 375.9422. 1HNMR: δ 03.08 (3H, s, CH3O), 6.75 (1H, d, J = 8.4, H-6), 7.28 (1H, t, J = 8.0, J = 8.4, H-5'), 7.40 (1H, dd, J = 8.0, J = 0.8, H-4'), 7.47 (1H, s, H-7), 7.93 (1H, s, H-4), and 13.82 (bs, NH, int. D2O).

5-Chloro-2-(methylsulfinyl)-5-(1-naphthoxy)-1H-benzimidazole (13). Into a stirred solution of 12 (0.50 g, 1.476 mmol) in 20 mL of CHCl3 was slowly added, dropwise, a solution of MCPBA (0.394 g, 1.37 mmol) in 15 mL of CHCl3 at 0-5°C. The progress of the reaction was monitored by TLC (CHCl3-MeOH, 97:3). When the reaction was completed, it was treated with a solution of NaHCO3 until pH 7. Afterwards, the mixture was extracted with CHCl3 (3 x 3 mL). The combined organic extracts were dried with anhydrous sodium sulphate, filtered and evaporated in vacuo to give 13 as a white soapy powder. The solid was recrystallized from ethanol-benzene 1:1 to give 0.381 g (72.43%) of a white powder. Mp 189-190°C. IR νmax 3422 (NH), 1048 (SO). MS (EI) (m/z): 356 (M+). HRMS (EI) calcd for C14H13ClN2O3S (M+) 356.0386. Found: 356.0380. 1HNMR: δ 3.08 (3H, s, CH3SO), 6.702 (1H, d, J = 7.5, H-2'), 7.376 (1H, s, H-4), 7.403 (1H, t, J = 8.1, H-3'), 7.568-7.638 (2H, m, H-6', H-7'), 7.69 (1H, d,
Studies on the Selective S-oxidation of Albendazole, Fenbendazole, Triclabendazole, and Other Benzimidazole Sulfides

was slowly added, under N2, CH3I (0.4 mL, 5.33 mmol) at 0°C. acetone and KOH (0.351 g, 6.27 mmol) in 0.5 mL of water, stirred, dark solution, of the reaction was monitored by TLC (CHCl3-MeOH, 95.5:0.5). Then, the mixture was stirred for 30 min at 10°C. The progress of the reaction was monitored by TLC (CHCl3-MeOH, 95.5:0.5). The NMR: δ 1.2, H-4), and 10.21 (bs, NH, int. D2O).

5-(Propylthio)-1H-benzimidazole-2-thiol (16). A stirred mixture of 15 (0.429 g, 1.912 mmol), EtOH (6 mL), KOH (0.233 g, 3.53 mmol) in water (1 mL) and CS2 (0.2 mL, 3.532 mmol) was heated at 50°C under N2 for 3 h. Then, the reaction was left 12 h at room temperature. The progress of the reaction was monitored by TLC (CHCl3-MeOH, 95.5:0.5). The yellow precipitate formed was poured into water and treated with 20% AcOH solution to pH 6. A stirred mixture of 15 (0.429 g, 1.912 mmol), SnCl2·2H2O (3.18 g, 14.13 mmol) with 20% AcOH solution to pH 6. The solid was separated by filtration, washed with water and air dried to obtain 16 (0.391 g, 74%) of a slightly yellow powder. Mp: 216.1-217.8°C. IR νmax 3439 (NH). MS (m/z) 16, 238 (M+). HRMS (EI) Calcd for C11H14N2S2 (M+) 238.0598, found: 238.0582. 1H-NMR: δ 0.99 (3H, t, J = 7.5, CH3CH2S), 2.84 (2H, t, J = 7.28, CH2CH2S), 7.14 (1H, s, H-7), 7.15 (1H, s, H-6), 7.25 (1H, m, H-4), and 9.55 (bs, NH, int. D2O).

Computational methodology

Complete optimization of the geometry of compound 17 was done with the program Spartan’02 [21] at level RHF/6-31G(d,p). The electrostatic potential map was calculated from the optimized geometry.

Acknowledgements

We are grateful to the Departamento Sistemas Biológicos from the UAM-X for the financial support for this work and to DGAPA, UNAM, for financing project IN 202101. We are also grateful to Rosa Isela del Villar, Georgina Duarte, Margarita Guzmán and Marisela Gutiérrez, from the Facultad de Química, UNAM, for the determination of the spectra.

References


Olivia Soria-Arteche, *et al.*