

Synthesis and characterization of novel N-substituted benzimidazole derivatives

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Abstract : Benzimidazole presently is the most pharmaceutically important scaffold. In the present paper, synthesis of a series of new N-substituted benzimidazole derivatives is described. In the first step precursor 5-nitro-1H-benzimidazole was obtained from the condensation of 4-nitro-1, 2-diamino benzene and ethyl formate in the presence of hydrochloric acid. Reaction of the derivative with various functionalized halides in basic medium led to the N-substituted benzimidazole derivatives. The structures of the synthesized compounds were characterized by ¹H, ¹³C NMR spectroscopy and high resolution mass spectrometry analysis.

(Keywords : benzimidazole, condensation, functionalized halides, N-substituted benzimidazole)

Introduction

Benzimidazole is a heterocyclic molecule commonly used as a building block in organic synthesis. It is formed by the condensation of orthophenylenediamine with carboxaldehyde and carboxylic acid. Many drugs such as thiabendazole, albendazole, mebendazole and flubendazole are used as proton pump inhibitions. Structural variations around benzimidazole nucleus by changing substituents have led to many derivatives with several biological activities including antioxidants¹⁻², antimicrobial³⁻⁷, antiviral⁶⁻¹⁰, anti-inflamm-matory¹¹⁻¹², anticancer¹³⁻¹⁹] and anti hypertensive²⁰⁻²².

Of all the structural variants, those affecting the first, second and fifth positions were found to be more significant. Consequently we in the present paper communicate a series of N-substituted benzimidazole derivatives.

Experimental

2. Materials and Methods

The solvents and reagents are of high quality and come from Aldrich Chemical or Fischer Scientific (France). The reactions were followed by TLC on pre-coated Merck 60 F254 silica gel plates and revealed using a UV lamp (6W, 254 nm, and/or 365 nm). The purification of the products was carried out on a Merck G60 silica gel column. Melting points (m.p° C) were determined using a temperature gradient (40°C-265°C) Kofler bench.

For all compounds, the Nuclear Magnetic Resonance (NMR) spectra of ¹H and ¹³C were recorded on a Bruker 300 advance device with deuterated chloroform (CDCl₃), acetone (Acetone-D₆) and dimethyl sulfoxide (DMSO-D₆) as the solvents, while tetramethylsilane (TMS) was used as an internal standard for chemical displacements (δ) expressed in ppm. The NMR spectra description use the following symbols: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quadruplet), m (multiplet), br (broad). The mass spectra were recorded on a JEOL JMS DX300 spectrometer in ESI mode (electrospray/quadripolar ionization or ESI mass).

Synthesis of 5-nitro-1H-benzimidazole (BZ1)

A mixture of 4-nitro-orthophenylenediamine (1 eq, 33 mmol), 30mL of ethyl formate and 6 mL of hydrochloric acid was refluxed under magnetic stirring for 48 hours. After cooling the reaction medium, the hydrochloric acid was neutralized with potassium carbonate (K₂CO₃).

The precipitate obtained was filtered and then washed with hexane. Compound **3a** was obtained as a purple powder in 95 % yield, m.p = 217-219°C. ¹H NMR (DMSO-D₆, 300 MHz), δ (ppm): 12.36 (s, 1H, NH), 8.29-7.76 (m, ⁴H, HAr). ¹³C NMR (DMSO-D₆, 75 MHz) δ (ppm): 145.15, 144.39, 136.49, 132.58, 120.08, 115.37, 111.6. HRMS (ESI) Calc. for C₇H₅N₃O₂ (M + H⁺) = 164.038 Found = 164.041.

5-nitro-2-mercapto-1H-benzimidazole (BZ2)

To a solution of 4-nitro o-phenylenediamine (1 eq, 46mmol) in 15mL of dimethylformamide (DMF) cooled in an ice bath, carbon disulfide (CS₂) (5 eq, 231 mmol) was added dropwise. The mixture was stirred at room temperature for 24 to 48 h and then 200 mL of water was added. The resulted precipitate was filtered, washed several times with water, and dried in an oven (80°C). The crude was recrystallized in a water/ethanol mixture (50/50).

Reaction time: 48 h, orange crystals, yield = 92 %, m.p = 264°C-266°C. ¹H NMR (DMSO-D₆, 300 MHz) δ (ppm): 12.54 (s, ¹H, NH), 8.30-7.50 (m, ⁴H, HAr), 2.50 (s, 1H, SH). ¹³C NMR (DMSO-D₆, 75 MHz) δ (ppm): 171.49, 142.48, 137.29, 132.15, 118.82, 109.11, 104.56. HRMS (ESI) Calc. for C₇H₅N₃O₂S (M + H⁺) = 196.010 Found = 196.0415.

2-thiomethyl-5-nitro-1H-benzimidazole (BZ3)

To compound **2** (1 eq, 6.66 mmol) dissolved in 10 mL of anhydrous ethanol, was added iodomethane (1.1 eq, 7.33 mmol). The mixture was brought to reflux under magnetic stirring. The reaction was followed by thin layer chromatography (TLC) for 7 h. At the end of reaction, ethyl acetate was added to the mixture. Then a precipitate was obtained, filtered and dissolved in ethanol Addition of a 30% sodium hydrogen carbonate solution to the mixture led to a new precipitate which was filtered, washed with water, wrung out and dried in an oven.

Yellow powder, yield=83%, m.p= 218-220°C. ¹H NMR (DMSO-D₆, 300 MHz) δ (ppm): 10.5 (s, ¹H, NH), 7.3-8.5 (m, 3H, HAr), 2.70 (s, 3H, CH₃). ¹³C NMR (DMSO-D₆, 75 MHz) δ (ppm): 144.25, 141.70, 139.75, 117.55, 112.98, 109.92, 13.68, HRMS (ESI) Calc. for C₈H₇N₃O₂S (M + H⁺) = 210.026 Found = 210.028.

2-(5-nitro-1H-benzimidazol-1-yl) ethanol (BZ4)

To benzimidazole derivatives (1 eq, 6 mmol) dissolved in 10 mL of DMSO, were added potassium carbonate (2 eq, 12 mmol) and functionalized 2-chloroethanol halides (4 eq, 24 mmol). The mixture was heated to 50°C with magnetic stirring and the reaction was monitored by TLC. At the end of the reaction, the mixture was then diluted with 50 mL of water. The mixture was extracted with dichloromethane (2 x 50 mL), dried over magnesium sulfate and the solvent was evaporated. The residue was purified by column chromatography with silica gel.

Reaction time: 4 h, orange crystals, yield = 52 %, m.p = 98°C-100°C. ¹H NMR (Acetone-D₆, 300 MHz) δ (ppm): 8.62-7.80 (m, 4H, HAr), 4.56 (s, ¹H, OH), 4.52 (t, J = 5.10 Hz, 2H, CH₂N), 3.99 (t, J = 5.10 Hz, 2H, CH₂OH). ¹³C NMR (Acetone-D₆, 75MHz) δ (ppm): 149.06, 120.50, 118.61, 117.80, 116.63, 111.79, 108.57, 61.47, 48.69. HRMS (ESI) Calc. for C₇H₅N₃O₂S (M+H⁺) = 208.064 Found = 208.061.

2-(2-thiomethyl-5-nitro-1H-benzimidazol-1-yl) ethanol (BZ3)

Reaction time: 24 h, yellow crystals, yield = 72 %, m.p = 152°C-154°C. ¹H NMR (DMSO-D₆, 300 MHz) δ (ppm): 7.5-8.5 (m, 3H, HAr), 5.00 (t, J = 5.40 Hz, ¹H, OH), 4.3 (m, 2H, CH₂N), 3.7 (m, 2H, CH₂O), 2.70 (s, 3H, CH₃). ¹³C NMR (DMSO-D₆, 75 MHz) δ (ppm): 162.23, 155.52, 147.37, 136.38, 117.13, 112.87, 110.03, 106.56, 59.00, 47.00, 14.28. HRMS (ESI) Calc. for C₁₀H₁₁N₃O₃S (M + H⁺) = 254.052 Found = 254.049.

Bis(5-nitro-benzimidazol-1-yl) methane (BZ4)

Reaction time: 4 h, yellow crystals, yield = 71 %, m.p > 266°C. ¹H NMR (Acetone-D₆, 300 MHz) δ (ppm): 8.62-7.80 (m, ⁸H, HAr), 6.74 (s, 2H, CH₂). ¹³C NMR (Acetone-D₆, 75 MHz) δ (ppm): 149.25, 147.70, 143.54, 132.14, 120.26, 115.98, 107.77, 148.06, 142.74, 137.01, 118.85, 118.12, 111.32, 52.87. HRMS (ESI) Calc. for C₁₅H₁₀N₆O₄ (M + H⁺) = 339.076 Found = 339.074.

Bis(2-thiomethyl-5nitro-1H-benzimidazol-1-yl) methane (BZ5)

Reaction time: 3 h, yellow crystals, yield = 68 %, m.p = 258°C-260°C. ¹H NMR (DMSO-D₆, 300 MHz) δ (ppm): 8.48-7.08 (m, 6H, HAr), 6.64 (s, 2H, CH₂), 2.73 (s, 6H, 2 CH₃). ¹³C NMR (DMSO-D₆, 300 MHz) δ (ppm): 150.13, 148.65, 142.49, 133.02, 122.13, 117.08, 107.01, 148.29, 143.61, 138.05, 119.03, 119.89, 113.07, 53.96, 14.26. HRMS (ESI) Calc. for C₁₇H₁₆N₄S₂ (M + H⁺) = 430.052 Found = 430.056.

1-(2-chloroethyl)-5-nitro-benzimidazole (BZ6)

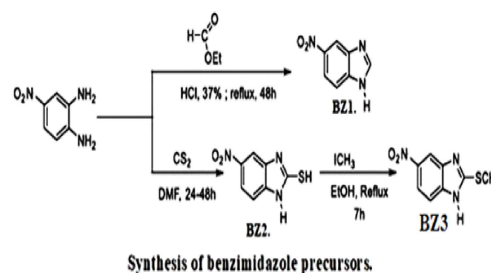
Reaction time: 5 h, beige powder, yield = 62 %, m.p = 132°C-134°C. ¹H NMR (Acetone-D₆, 300 MHz) δ (ppm): 8.50 (s, 1H, CH=N), 8.64-7.89 (m, 3H, HAr), 4.94 (t, J = 5.7 Hz, ¹H, CH₂aN), 4.87 (t, J = 5.7 Hz, 1H, CH₂bN), 4.20 (m, 2H, CH₂Cl). ¹³C NMR (Acetone-D₆, 75 MHz) δ (ppm): 148.86, 120.93, 118.96, 118.20, 116.92, 111.62, 108.33, 44.00. HRMS (ESI) Calc. for C₉H₈N₃O₃Cl (M + H⁺) = 226.031 Found = 226.034.

1, 2-bis (2-thiomethyl-5-nitro-1H-benzimidazol-1-yl) ethane (BZ7)

Reaction time: 24 h, green crystals, yield = 20 %, m.p = 128°C-130°C. ¹H NMR (DMSO-D₆, 300 MHz) δ (ppm): 8.51-7.12 (m, 6H, HAr), 5.76 (d, J = 7.1 Hz, 2H, CH₂N), 5.50 (d, 6.9 Hz, 2H, CH₂Cl), 2.71 (s, 6H, 2 SCH₃). ¹³C NMR (DMSO-D₆, 75 MHz) δ (ppm): 147.33, 142.30, 139.01, 134.24, 127.33, 118.35, 117.91, 117.58, 113.16, 110.58, 106.52, 110.33, 110.24, 14.49, 14.43. HRMS (ESI) Calc. for C₁₈H₁₆N₆O₄S₂ (M + H⁺) = 445.067 Found = 445.070.

Results and Discussion

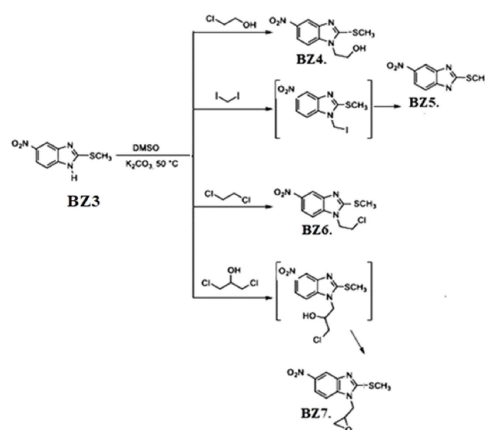
The synthesis of N-substituted benzimidazole derivatives was carried out by first preparing the precursor BZ1 by the procedure described by Wagner and Millet²³. The derivative BZ2 was obtained according to the Van Allan method²⁴ by the reaction of 4 - nitro orthophenylenediamine with carbon disulfide (CS₂) in 92% yield. It was methylated with methyl iodide (ICH₃) under reflux of ethanol²⁵ to give BZ3.



BZ3 was subjected to N deprotonation reaction in basic medium. Then N-, alkylated derivatives of benzimidazole BZ4 to BZ8 were obtained in a substitution reaction on the nitrogen via benzimidazolyl anion and various halogenated functionalities with one to three carbon atoms, (CH₂)_n, n=1-3 as shown in the following scheme.

Reaction of BZ3 with 2-chloroethanol led to the N-substituted derivative BZ4 in 70% yield. The reaction with diiodomethane under the same condition leads to the production of BZ5. The results can be explained by the fact that since iodine is a bulky and good initiator, the resulting N-alkylated product is transformed into an intermediate that undergoes a duplication reaction in the presence of a second benzimidazolyl anion to give BZ5.

When diiodomethane was replaced by 1, 2-dichloroethane, the N-substituted compound BZ6 is obtained whose yield was higher than that of BZ5.



Synthesis of N-alkylated benzimidazole derivatives.

The structure of various benzimidazole derivatives BZ1 to BZ7 was confirmed by ^1H , ^{13}C NMR spectroscopic analysis and HRMS.

Indeed, in the ^1H NMR spectra of the different compounds, it was clearly observed that the substitution on the nitrogen atom by the absence of a peak between 11 and 12 ppm characteristic of the NH proton group and also the appearance of a novel peak between 4 and 6 ppm characteristic of the methylene proton bound to the nitrogen.

References

- Göker, C. Ku^o, DW.Boykin, et al. *Bioorg med Chem.* 10(8) : 2589 (2002).
- C. Kus, G. Ayhan-Kilcigil, BC. Eke, et al. *Arch Pharmacol Res.* **27**(2):156-63(2004).
- Ayhan-Kılıçgil G, Altanlar N. *Farmaco.* **58** (12):1345 (2003).
- Pawar NS, Dalal DS, Shimpi SR, et al. *Eur j Pharm Sci.* **21** (2-3):115 (2004).
- 5.Özden S, Atabey D, Yıldıız S, et al. *Bioorg Med Chem.* 13(5):1587 (2005)
- Sharma D, Narasimhan B, Kumar P, et al. *Jenzyme inhib Med Chem.* 24(5):1161 (2009)
- Rida SM, El-Hawash SA, Fahmy HT, et al. *Arch Pharmacol Res.* 29(10):826 (2006).
- Tonelli M, Novelli F, Tasso B, et al. *Bioorg Med Chem.* **22**(17):4893 (2014)
- Tonelli M, Simone M, Tasso B, et al. *Bioorg Med Chem.* 18(8):2937(2010)
- Pan T, He X, Chen B, et al. *Eur j med chem.* 2015;95:500-13.
- Veerasamy R, Roy A, Karunakaran R, et al. An overview. *Pharmaceuticals.* 2021; 14(7):663.
- Chen G, Liu Z, Zhang Y, et al. *ACS med chem lett.* 2013;4(1):69-74.
- Achar KC, Hosamani KM, Seetharamareddy HR. *Eur J Med Chem.* **45**(5):2048 (2010).
- Kumar N, Sharma CS, Ranawat MS, et al. *J Pharm Investig.* 45(1):65 (2015)
- Romero-Castro A, León-Rivera I, Ávila-Rojas LC, et al. *Arch Pharmacol Res.* 34(2): 181 (2011).
- Demirayak S, Kayagil I, Yurttas L. *Eur j med chem.* 46(1):411 (2011)
- Refaat HM. *Eur j med chem.* **45**(7):2949 (2010)
- Repicky A, Jantova S, Cipak L. *Cancer lett.* 2009; 277(1):55-63.
- Penning TD, Zhu GD, Gandhi VB, et al. *J med chem.* 2009;52(2):514-23.
- Zhang Y, Xu J, Li Y, et al. *Design, Chem biol drug des.* 2015; 85(5):541-8.
- Zhu W, Da Y, Wu D, et al. *Bioorg Med Chem.* 2014; 22(7):2294-302.
- Yadav G, Ganguly S. *Eur j med chem.* ; 97:419 (2015)
- Wagner EC, Millett WH. *Benzimidazole. Org synth.* 2003;19:12.
- VanAllan JA, Deacon BD. 2 Mercapto benzimidazole - 2 - Benzimidazolethiol. *Org Synth.* ; 30:56 (1950).
- Iddon B, Kutschy P, Robinson AG, et al. *J Chem Soc Perkin Trans 1.* (22):3129 (1992).

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