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Synthesis, structural characterization and antimicrobial activity of silver(I) complexes with 1-benzyl-1*H*-tetrazoles

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Abstract

Herein, we report the synthesis and structural characteristics of three tetrazole-containing compounds, 1-benzyl-1*H*-tetrazole (bntz), 1-benzyl-1*H*-tetrazol-5-amine (bntza) and 1-(4-methoxybenzyl)-1*H*-tetrazol-5-amine (mbntza) and the corresponding silver(I) complexes of the general formula $[Ag(NO_3\text{-}O)(L\text{-}N4)_2]_n$, L = bntz (**1**), bntza (**2**) and mbntza (**3**). Silver(I) complexes **1** – **3** and 1-benzyl-1*H*-tetrazoles have been studied in detail by NMR, IR and UV-Vis spectroscopic methods and the structures of **1** and **2** have been determined by single-crystal X-ray diffraction analysis. The results of these analyses revealed a monodentate coordination of the ligands to Ag(I) ion *via* the N4 tetrazole nitrogen. The antimicrobial potential of silver(I) complexes **1** – **3** was evaluated against the broad panel of Gram-positive and Gram-negative bacteria and fungi, displaying their remarkable inhibiting activity with MIC (minimal inhibitory concentration) values in the range 2 – 8 and 0.16 – 1.25 μg/mL (3.8 – 16.3 and 0.31 – 2.15 μM), respectively. On the other hand, 1-benzyl-1*H*-tetrazoles used for the synthesis of the silver(I) complexes were not active against the investigated strains, suggesting that the activity of the complexes originates from the Ag(I) ion exclusively. Moreover, silver(I) complexes **1** – **3** have good therapeutic potential, which can be deduced from their moderate cytotoxicity on the human fibroblast cell line MRC5, with IC_{50} values falling in the range 30 – 60 μg/mL (57.7 – 103.4 μM).

Keywords: 1-Benzyl-1*H*-tetrazoles, Silver(I) complexes, Structural characterization, Antimicrobial activity, Cytotoxicity

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Synthesis of 1-benzyl-1*H*-tetrazoles

1-Benzyl-1H-tetrazole (bntz)

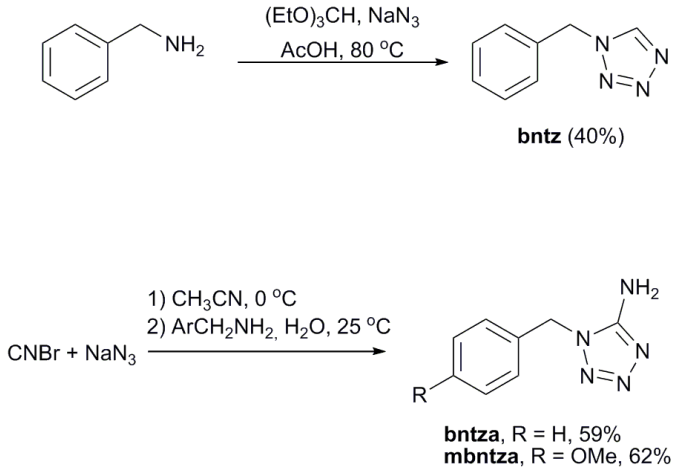
The reaction tube was charged with benzylamine (1.0 mL, 9.3 mmol), $(EtO)_3CH$ (2.5 mL, 14.9 mmol, 1.6 equiv), NaN_3 (910 mg, 14.0 mmol, 1.5 equiv) and glacial AcOH (8.3 mL) [1]. The reaction tube was closed and heated at 80 °C for 16 hours. After the time has passed, the volatile materials were removed under the reduced pressure. The remaining residue was dissolved in H_2O (20 mL) and the mixture was extracted with EtOAc (2 × 30 mL). The organic solution was washed with 1 M aqueous solution of HCl, water, saturated solution of $NaHCO_3$ and brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the hexane was added to the remaining oil. The mixture was stirred for 5 min and the solvent was removed under reduced pressure. The remaining residue was treated with hexane one more time, which led to crystal formation. The product was dried under the reduced pressure to afford bntz as a yellow crystalline solid.

1-Benzyl-1H-tetrazol-5-amine (bntza)

In a flame-dried flask, CNBr (1.940 g, 18.3 mmol, 2 equiv) was dissolved in dry CH_3CN (15 mL) at 0 °C. NaN_3 (5.675 g, 87.3 mmol, 9.5 equiv) was added at the cooled solution and the resulting mixture was stirred at 0 °C for 4 h [2]. The precipitate was filtered on a Hirsch funnel and the filtrate was added dropwise to a stirred emulsion of benzylamine (1 mL, 9.2 mmol) in H_2O (9 mL) at 0 °C. The resulting mixture was stirred at room temperature for 48 h. After the time has passed, the solvents were removed under the reduced pressure. The remaining residue was filtered and washed with H_2O and CH_3CN. The product was dried under the reduced pressure to afford bntza as a colorless solid.

1-(4-Methoxybenzyl)-1H-tetrazol-5-amine (mbntza)

Following the procedure described for bntza [2], compound mbntza was obtained from 4-(methoxyphenyl)methanamine as a colorless crystalline solid.



Scheme S1. Schematic presentation of the reactions for the synthesis of 1-benzyl-1*H*-tetrazoles [1,2].

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[2] Y. Satoh, N. Marcopulos, Tetrahedron Lett. 36 (1995) 1759-1762.