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Pyridine-Imidazlolium Salts: Oxidatively Cleavage of N-C Bond via Nitration

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Abstract: Azaheterocycles derivatives with pyridine-imidazole skeleton are compounds of great value for medicinal chemistry. We report herein the nitration of 1,1′-(pyridine-2,6-diylbis(methylene))bis{3-[2-(4-nitrophenyl)-2-oxoethyl]-1*H*-imidazol-3-ium} bromide using a typical mixture of nitric and sulphuric acid. The nitration occur with the oxidative cleavage of N–C bond between imidazolium ring and methylene group.

Keywords: nitration; azaheterocycles; N–C bond cleavage; pyridine-imidazolium

1. Introduction

In the past decades five and six member ring azaheterocycles compounds, especially imidazole and (di)azine, became invaluable scaffolds in drug designing because of their large variety of biological activities, such as anticancer, antimicrobial (antibacterial, antifungal, antitubercular), antimalarial, anti-inflammatory, antidepressant, analgesic, antihypertensive etc. [1–7].

Taking into consideration our expertise in the area of obtaining new biologically active compounds with antimicrobial activity [8–14] using cycloimmonium ylides chemistry [15–21], we decided to study the reactions of pyridine-imidazolium salts with nitric acid.

2. Results and Discussion

In this respect, we perform the nitration of 1,1'-[pyridine-2,6-diylbis(methylene)]bis{3-[2-(4-nitrophenyl)-2-oxoethyl]-1*H*-imidazol-3-ium} bromide **1**, using a typical mixture of nitric and sulphuric acid, Figure 1.

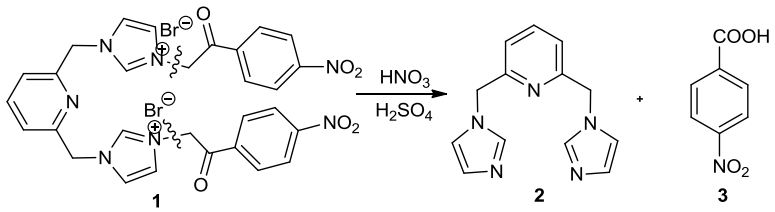

Figure 1. The nitration of 1,1′-[pyridine-2,6-diylbis(methylene)]bis{3-[2-(4-nitrophenyl)-2-oxoethyl] -1*H*-imidazol-3-ium} bromide.

Our expectation was to have a nitration in the 3-position of pyridine ring or in the 4-position of the imidazole moiety. Instead of this an unexpected oxidative cleavage N–C bond between imidazolium ring and methylene group took place, with the formation of

2,6-bis[(1*H*-imidazol-1-yl)methyl]pyridine **2** and 4-nitrobenzoic acid **3**. The structures of compounds were proven by spectroscopic analysis: ^{1}H-NMR, ^{13}C-NMR, and two-dimensional experiments 2D-COSY, 2D-HMQC, 2D-HMBC.

In conclusions, nitration of 1,1′-[pyridine-2,6-diylbis(methylene)]bis{3-[2-(4-nitrophenyl)-2-oxoethyl]-1*H*-imidazol-3-ium} bromide occur with the oxidative cleavage of N–C bond between imidazolium ring and methylene group, with the formation of two side products 2,6-bis[(1*H*-imidazol-1-yl)methyl]pyridine **2** and 4-nitrobenzoic acid **3**.

3. Materials and Methods

3.1. Instrumentation

All the reagents and solvents were purchased from commercial sources (Sigma Aldrich and Merck, Darmstadt, Germany) and used without further purification. Melting points were recorded on an Electrothermal MEL-TEMP (Barnstead International, Dubuque, IA, USA) apparatus in open capillary tubes and are uncorrected. Analytical thin-layer chromatography was performed with commercial silica gel plates 60 F254 (Merck) and visualized with UV light. The NMR spectra were recorded on a (Bruker, Vienna, Austria) Advance III 500 MHz spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C. Chemical shifts were reported in delta (δ) units, part per million (ppm) and coupling constants (*J*) in Hz.

2,6-Bis[(1*H*-imidazol-1-yl)methyl]pyridine **2**, was initially synthetized by Garrison and Co [22]; in the supporting information of the paper all the data concerning the compound can be found for comparison.

4-Nitrobenzoic acid **3**, is a commercially available compound and relevant data can be found in the Sigma-Aldrich catalog [23].

3.2. Nitration of Pyridine-Imidazolium Salts

Concentrated nitric acid (HNO_3 65%, p.a.) (4.89 mmol, 9.78 equiv., 0.22 mL) was added dropwise over the undissolved quaternary salt **1** (0.5 mmol, 1 equiv., 0.36 g) at 0 °C (ice bath) under vigorous stirring, until the entire precipitate has been dissolved (10 min) completely. Concentrated sulfuric acid (H_2SO_4 98%) (3.825 mmol, 7.65 equiv., 0.21 mL) was added dropwise, at 0 °C (ice bath), over the reaction mixture. The resulting solution was stirred at room temperature for 30 min, and after that heated at 130 °C for 2 h. The nitrogen oxides released were bubbled into a water bath. The reaction was processed by neutralization with a saturated $NaHCO_3$ solution (0.95 mL). The formed precipitate was collected by filtration, washed with distilled H_2O (5–7 mL), and dried in vacuum, obtaining 2,6-bis[(1*H*-imidazol-1-yl)methyl]pyridine **2** as a white powder.

From the aqueous phase the extraction was performed with ethyl acetate (3 × 20 mL), the phase was separated and the organic layer was dried over sodium sulphate. After filtration, the solution was left overnight, resulting in the formation of a yellow acicular precipitate, 4-nitrobenzoic acid

2,6-Bis[(1H-imidazol-1-yl)methyl]pyridine (**2**). White powder, m.p. 106–107 °C. Yield 32%. ^{1}H-NMR (500 MHz, DMSO) (ppm): 7.78 (t, 1H, 3*J* = 8.0 Hz, H_4), 7.74 (s, 2H, $2H_{2'}$), 7.19 (as, 2H, $2H_{5'}$), 7.03 (d, 2H, 3*J* = 8.0 Hz, $2H_3$), 6.92 (as, 2H, $2H_{4'}$), 5.28 (s, 4H, 2(-CH_2-). ^{13}C-NMR (125 MHz, DMSO) (ppm): 156.7 ($2C_2$), 138.5 (C_4), 137.7 ($2C_{2'}$), 128.6 ($2C_{4'}$), 120.4 ($2C_3$), 119.8 ($2C_{5'}$), 51.13 (2(-CH_2-)).

4-Nitrobenzoic Acid (**3**). Yellow acicular crystals, m.p. 237–238 °C. Yield 41%. ^{1}H-NMR (400 MHz, DMSO) (ppm): 13.67 (brs, 1H, -COOH), 8.30 (d, 2H, 3*J* = 7.6 Hz, $2H_3$), 8.15 (d, 2H, 3*J* = 7.6 Hz, $2H_2$). ^{13}C-NMR (100 MHz, DMSO) (ppm): 165.8 (-COOH), 150.0 (C_4), 136.3 (C_1), 130.7 ($2C_3$), 123.7 ($2C_2$).

Supplementary Materials: ^{1}H- and ^{13}C- NMR spectra for compounds **2** and **3** are available online.

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Conflicts of Interest: The authors declare no conflict of interest.

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