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Short Note

4,4′-(Pyrrolo[3,2-*b*]pyrrole-1,4-diyl)dianiline

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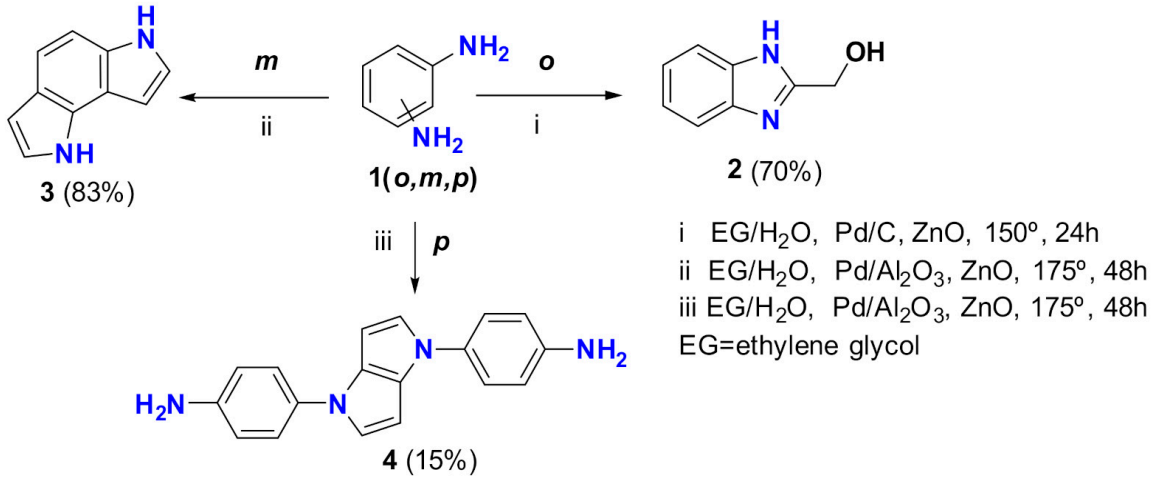
Abstract: 4,4′-(Pyrrolo[3,2-*b*]pyrrole-1,4-diyl)dianiline was synthesized in one step from benzene-1,4-diamine and ethylene glycol with Pd/Al_2O_3 and ZnO. The title compound was characterized by means of NMR techniques and HRMS mass spectrometry.

Keywords: heterocycles; acceptorless dehydrogenative condensation

1. Introduction

Nitrogen-containing heterocycles, such as pyridine, quinoline, and pyrrole, are found to be present in the vast majority of drugs; therefore, they are considered to be distinctive building blocks in the pharmaceutical industry. An analysis of the database of U.S. FDA approved drugs has pointed out that 59% of small molecule drugs contain a nitrogen-containing heterocycle [1].

In previous works employing *ortho* or *meta* benzene-diamine **1** (*o*, *m*), compounds **2** and **3** were prepared in excellent yields [2,3] (Scheme 1). Diamine **1** reacted with ethylene glycol, with Pd/C or Pt/Al_2O_3 as the catalyst. Importantly, ZnO was also required as the co-catalyst. These reactions were performed at 150 or 175 °C during 24–48 h. The formation of compounds **2** and **3** was explained by Borrowing Hydrogen [4–6] /Hydrogen Autotransfer [7] (BH/HA)-based mechanisms. Specifically, Acceptorless Dehydrogenative Condensation (ADC) [8,9] is responsible for the formation of those compounds. In this work, we report the results obtained with the *para* isomer of diamine **1**.

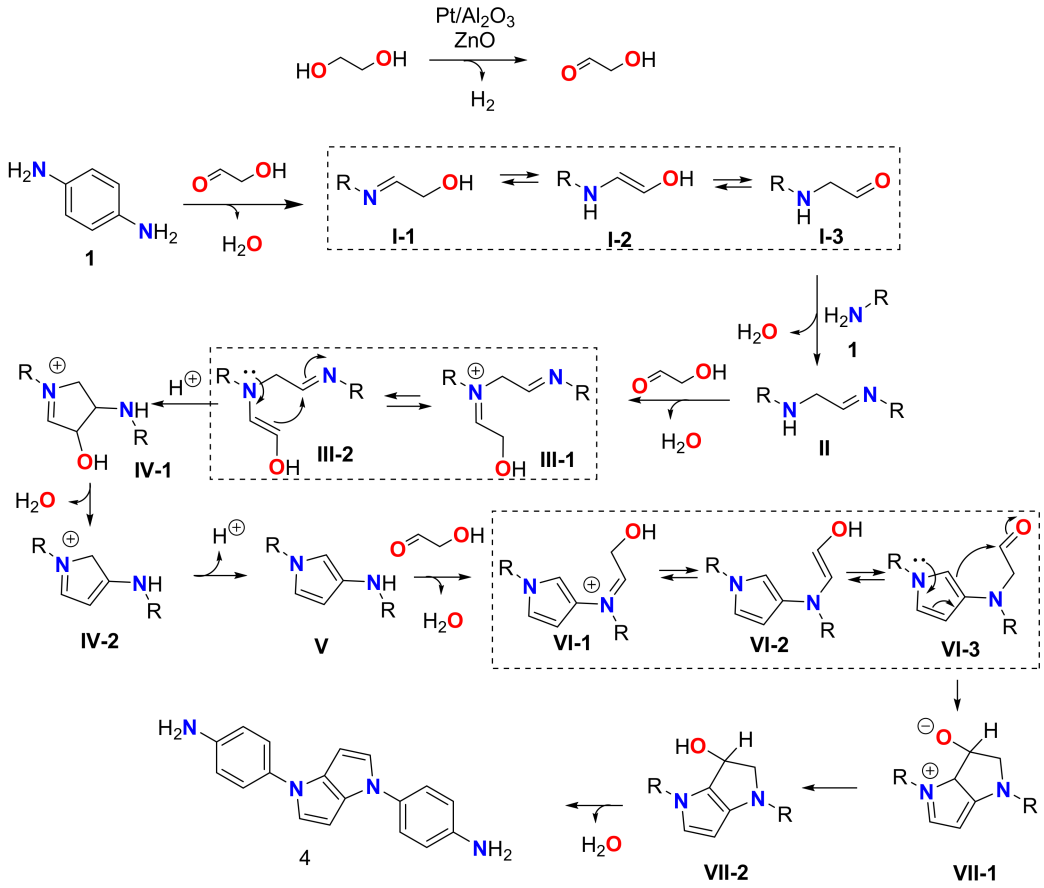


Scheme 1. Previous results and product obtained in this work.

2. Results

The reaction between benzene-1,4-diamine (**1**) with ethylene glycol/water in the conditions described by our research group resulted in intractable mixtures. However, when neat ethylene

glycol was used as the solvent, we isolated by chromatography an oil that HRMS gives, with a molecular ion at 289.1442 amu corresponding to a $C_{18}H_{16}N_4$ formula. The ^{1}H NMR showed two AB systems, one with two doublets at 6.71 and 7.27 ppm (J = 9 Hz, 8H), and the second at 6.27 and 6.96 ppm (J = 3 Hz, 4H). In the ^{13}C NMR, only seven aromatic signals were observed—four CH and three quaternary carbons. Bidimensional correlations (H,H COSY, HSQC, and HMBC; see Supplementary Materials) allowed the structural elucidation of this compound as 4,4′-(pyrrolo [3,2-*b*]pyrrole-1,4-diyl)dianiline (**4**). Pyrrolo[3,2-*b*]pyrrole-containing compounds have many important applications in different fields. [10] The compound **4** was formed with two units of benzene-1,4-diamine and three units of ethylene glycol. A plausible mechanism based on an ADC process is proposed in Scheme 2.



Scheme 2. Mechanism proposal. Dashed rectangles indicate tautomeric equilibriums.

As can be seen, the dehydrogenation of ethylene glycol provides in situ glyceraldehyde. Condensation with **1** affords imine **I-1.** Intermediates **I-1**, **I-2**, and **I-3** are under tautomeric equilibrium. A second imine formation between amino aldehyde **I-3** and **1** provides intermediate **II**. After this, a second molecule of glyceraldehyde reacts to produce **III-1**. **III-1** and **III-2** are, again, under tautomeric equilibrium; however, **III-2** can undergo intramolecular enamine/imine addition, yielding cyclic intermediate **IV-1**. Water elimination affords structure **IV-2** that, after deprotonation, generates amino pyrrole **V**. A third molecule of glyceraldehyde produces **VI-1** that also presents a tautomeric equilibrium towards **VI-2** and **VI-3**. Intramolecular electrophilic aromatic substitution in **VI-3** generates intermediate **VII-1**, after re-aromatization of **VII-2** compound **4** is obtained. A final water elimination yields compound **4**. The whole reaction involves two molecules of **1** and three of ethylene glycol. Water and molecular hydrogen are the unique side products. The overall yield was low (15%); however, by thin layer chromatography and NMR, unreacted diamine **1** could be identified.

3. Materials and Methods

Starting materials, if commercially available, were purchased and used as such. ZnO nanoparticles were purchased from Sigma Aldrich (Europe) (<100 nm particle size (DLS), <0 nm average particle size (APS), 20 wt % in H_2O). ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at 300 and 75 MHz in $CDCL_3$. Chemical shifts are reported in δ units, parts per million (ppm), and were measured relative to the signals for residual chloroform. Coupling constants (*J*) are given in Hertz (Hz). Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). HRMS were recorded using TOF electrospray ionization (ESI-positive). IR spectra were recorded using FT-IR ATR, the solvents used were of spectroscopic or equivalent grade. Water was twice distilled and passed through a Millipore apparatus. All reaction mixtures were filtered through a 0.45 μm PTFE 25 mm syringe filter.

*Synthesis of 4,4′-(Pyrrolo[3,2-b]pyrrole-1,4-diyl)dianiline (**4**)*

Benzene-1,4-diamine 1 (2 mmol), 1.7% of Pt/Al_2O_3 (132.5 mg), 4.5% of ZnO nanoparticles (21.5 μL), and ethylene glycol (4 mL) were mixed manually inside a 50 mL quick-thread glass reaction tube. The tube was sealed with an Easy-On PTFE cap and put into a Carousel 12 Plus reaction station at 175 °C for 48 h. The reaction mixture was cooled to room temperature, and it needed to be opened carefully to depressurize the tube. After that, 25 mL of ethyl acetate was added, and the crude was filtered through a 0.45 μm PTFE filter. The reaction mixture was extracted with distilled water (3 × 10 mL), and the organic layer was dried with Na_2SO_4, filtered, and concentrated to afford the reaction crude that was checked by ^1H-NMR. The crude reaction product was purified by chromatography (Silica gel, Hexane/Ethyl Acetate from 3:1 to 1:3 *v:v*) as a brown oil identified as the 4,4′-(pyrrolo[3,2-*b*]pyrrole-1,4-diyl)dianiline (**4**) (47 mg, yield 15%). ^1H-NMR (300 MHz, Cl_3CD); δ: 7.26 (d, J = 9 Hz, 4H), 6.95 (d, J = 3 Hz, 2H), 6.70 (d, J = 9 Hz, 4H), 6.27 (d, J = 3 Hz, 2H), 0.7 (sa,4H). ^{13}C-NMR (75 MHz, Cl_3CD); δ: 143.4(C), 133.2(C), 128.1(C), 121.3(CH), 121.1(CH), 116.1(CH), 93.6(CH). HRMS: [M + H^+] calc. for C18H16N4: 289.1448; found: 289.14425. IR (ATR): 3771, 2922, 2851, 1632, 1516, 1421, 1273, 1177, 825, 689 cm^{-1}. UV-vis (5×10^{-4} M in methanol): λ_{max} 206, 240, and 298 nm.

Supplementary Materials: The following are available online. Figure S1: ^1H NMR spectrum of **4**, Figure S2: ^{13}C NMR and DEPT 135 spectrum of **4**, Figure S3: H, H COSY of **4**, Figure S4: HMBC of **4**. Figure S5 HSQC of **4**. Figure S6 HRMS Mass spectrum of **4**. Figure S7 IR (ATR) of **4**. Figure S8: UV/Vis Spectra of **4**.

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

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