Short Note

1-(2,5-Dimethoxy-4-nitrophenyl)piperidine and 1-(2,5-dimethoxy-4-nitrophenyl)pyrroridine

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1-(2,5-Dimethoxy-4-Nitrophenyl)piperidine and 1-(2,5-Dimethoxy-4-Nitrophenyl)pyrroridine

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Abstract: Treatment of the non-purified mixture of dinitro isomers obtained from the nitration of 1,4-dimethoxybenzene with piperidine, led to the isolation of novel but minor adduct, 1-(2,5-dimethoxy-4-nitrophenyl)piperidine (**2b**) in 15% yield. Yields of nucleophilic aromatic substitution adducts are high when using purified 1,4-dimethoxy-2,5-dinitrobenzene (**1b**) with piperidine and pyrrolidine to give **2b** and 1-(2,5-dimethoxy-4-nitrophenyl)pyrrolidine (**3b**) in 76% and 82%, respectively.

Keywords: benzimidazolequinone; nitration; nitrobenzene; nucleophilic aromatic substitution

1. Introduction

1,4-Dimethoxy-2,3-dintrobenzene (**1a**) is the precursor for the synthesis of potent bioreductive anti-cancer agents [1,2], the benzimidazole-4,7-diones [3,4] and ring-fused benzimidazolequinones [5,6]. For example, pyrido[1,2-*a*]benzimidazolequinone (Figure 1), which is 300 times more cytotoxic than the clinical anti-tumor drug, mitomycin C under hypoxic conditions, associated with solid tumors [5,7].

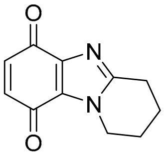
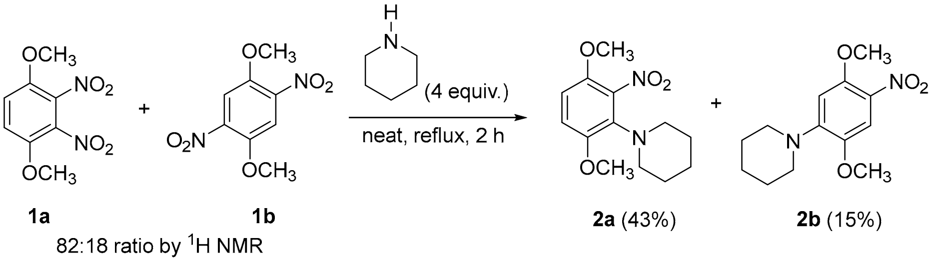


Figure 1. Pyrido[1,2-*a*]benzimidazolequinone [5,7].

The nitration of 1,4-dimethoxybenzene gives 2,3-dinitrobenzene **1a** as the major product with isomeric, 1,4-dimethoxy-2,5-dinitrobenzene (**1b**) separated by column chromatography [8], or recrystallization [9].

2. Results and Discussion

To expediate the synthesis of pyrido[1,2-*a*]benzimidazolequinone (Figure 1) [7], the non-purified mixture of dinitro isomers **1a** and **1b** from the nitration of 1,4-dimethoxybenzene was subjected to heating in piperidine under reflux giving 1-(3,6-dimethoxy-2-nitrophenyl)piperidine (**2a**) and 1-(2,5-dimethoxy-4-nitrophenyl)piperidine (**2b**) in 43% and 15% yield respectively (Scheme 1).



Scheme 1. Yields of adducts **2a** and **2b** after dry column vacuum chromatography (DCVC).

The NMR spectra show distinct differences in the aromatic region for isomers **2a** and **2b**. The *para*-arrangement of the piperidinyl- and nitro-substituents of **2b** gives well-separated singlets (at 6.48 and 7.55 ppm for H-6 and H-3, respectively, Figure 2b), in comparison to the two aromatic doublets (at 6.72 and 6.84 ppm, *J* = 9.1 Hz, of 4,5-H) in the ^{1}H NMR spectrum of **2a** (Figure 2a [7]).

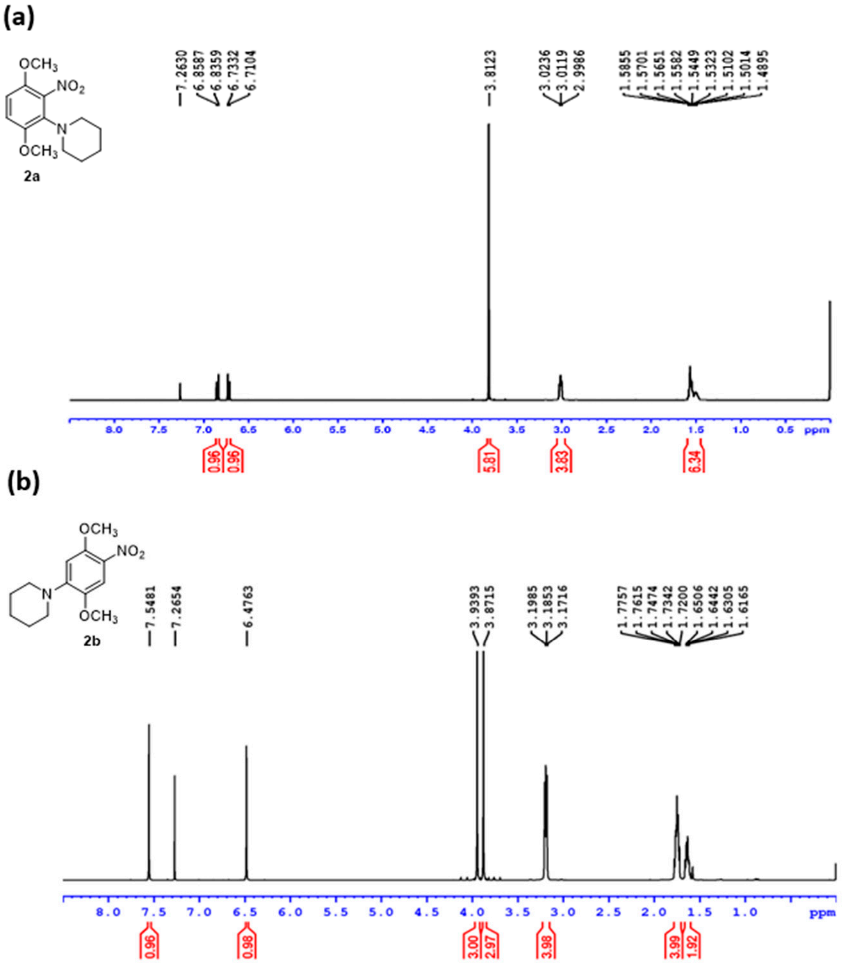
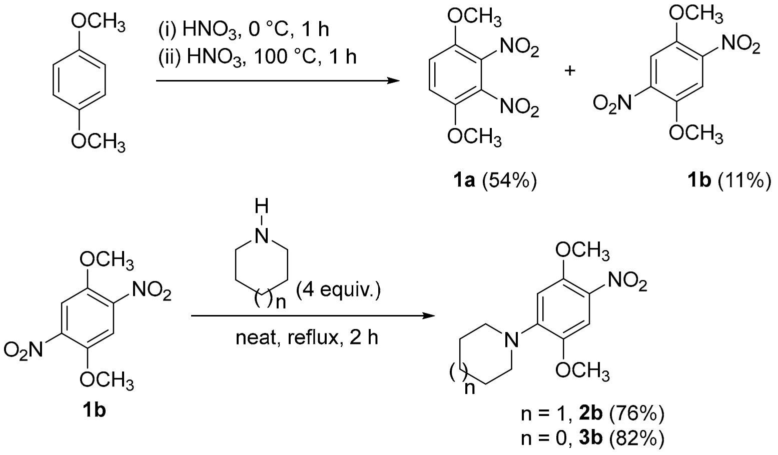


Figure 2. ^{1}H NMR spectra of **(a) 2a** [7], and **(b)** novel isomer **2b**.

Given that nucleophilic aromatic substitution adducts of 2,5-dintrobenzene **1b** are novel (see below), column chromatography was used to separate **1b** (11%) on gram scale from major isomer **1a** (54%) after nitration of 1,4-dimethoxybenzene (Scheme 2). Heating purified **1b** in piperidine at reflux gave 1-(2,5-dimethoxy-4-nitrophenyl)piperidine (**2b**) in 76% yield with the analogous reaction with pyrrolidine giving 1-(2,5-dimethoxy-4-nitrophenyl)pyrrolidine (**3b**) in 82% yield. The pyrrolidine adduct **3b** was isolated without the requirement for purification (chromatography or recrystallization), with only evaporation of the reaction mixture carried out after EtOAc-brine extraction. There is no literature data available for adducts **2b** and **3b**, and thus the compounds are assumed to be new, although **3b** is listed in the catalogues of two Chinese suppliers [10,11].



Scheme 2. Synthesis 1,4-dimethoxy-2,5-dintrobenzene (**1b**) and derived novel adducts **2b** and **3b**.

3. Materials and Methods

3.1. Materials and Measurements

All chemicals were sourced from commercial suppliers and used without purification, including piperidine (99%, Thermo scientific), and pyrrolidine (98%, TCI). Nitric acid (69%, EMSURE®, Merck) and 1,4-dimethoxybenzene (9.95 g, 72.0 mmol, ReagentPlus® 99%, Sigma-Aldrich) gave the mixture of dinitro-isomers (11.67 g, 71%, ratio in Scheme 1), according to this literature procedure [9]. Thin layer chromatography (TLC) was performed on Merck TLC silica gel 60 F254 plates using a UV lamp (254 nm) for visualization. Flash chromatography and dry column vacuum chromatography (DCVC) were performed using Fluka silica gel 60 (particle size 35–70 µm) and Milipore silica gel 60 (particle size 15–40 µm), respectively, using gradient elution of EtOAc (Fischer Scientific, ≥ 99%) and hexanes (Fischer Scientific, bp 40–60 °C), as eluent. The organic extract was dried using $MgSO_4$ (anhydrous, Fisher Scientific, Extra Pure). Melting point was measured on a Stuart Scientific melting point apparatus, SMP3. Infrared spectrum (IR) was recorded on the solid samples using a Perkin-Elmer Spec 1 with ATR attached, where s, m, and w are strong, medium, and weak signals, respectively. All NMR spectra were recorded in $CDCl_3$ (Eurisotop®, 99.8% atom D) using a Bruker Avance III 400 MHz spectrometer equipped with a 5 mm $BBFO^+$, broadband autotune probe and controlled with TopSpin 3.5.7 acquisition software and IconNMR 5.0.7 automation software Copyright © 2017 Bruker BioSpin GmbH. Chemical shifts are in ppm relative to tetramethylsilane (TMS). ^{13}C NMR spectra were acquired at 100 MHz with complete proton decoupling. NMR assignments are supported by DEPT-135, ^1H–^1H COSY and ^1H–^{13}C edited HSCQ correlation. HRMS spectra of compounds **2b** and **3b** were obtained at the National Mass Spectrometry Facility at Swansea University using a Waters Xevo G2-S mass spectrometer with an Atmospheric Solids Analysis Probe (ASAP). The precision of all accurate mass measurements was better than 5 ppm.

3.2. Synthesis of 1-(2,5-dimethoxy-4-nitrophenyl)piperidine (2b)

The mixture of 2,3-dintrobenzene **1a** and 2,5-dintrobenzene **1b** (82:18% ratio by ^1H NMR, 0.800 g, 3.5 mmol) and piperidine (1.38 ml, 14.0 mmol) was stirred at reflux for 2 h. EtOAc (20 ml) was added to the cool red residue, which was washed with brine (3 x 30 ml). The organic layer was dried ($MgSO_4$) and evaporated to dryness. The residue was purified by DCVC using gradient elution of EtOAc/hexane to give 1-(3,6-dimethoxy-2-nitrophenyl)piperidine (**2a** [7]) (0.400 g, 43%), as a yellow solid, R_f 0.51 (3 : 7 EtOAc : hexane); and the title compound **2b** (0.140 g, 15%) as an yellow solid; mp 126–127 °C; R_f 0.30 (3 : 7 EtOAc : hexane); ν_{max} (neat, cm^{-1}) 2929 (m), 2853 (w), 1610 (m), 1571 (m), 1509 (s), 1444 (m), 1312 (s), 1266 (s), 1243 (s), 1210 (s); δ_H (400 MHz, $CDCl_3$) 1.62-1.65 (m, 2H, 3′-CH_2), 1.72-1.78 (m, 4H, 2′-CH_2), 3.19 (t, 4H, J = 5.4 Hz, 1′-CH_2), 3.87 (s, 3H, 2-CH_3), 3.94 (s, 3H, 5-CH_3), 6.48 (s, 1H, 6-H), 7.55 (s, 1H, 3-H); δ_C (100 MHz, $CDCl_3$) 24.2 (3′-CH_2), 25.9 (2′-CH_2), 51.4 (1′-CH_2), 56.2 (CH_3), 56.9

(CH_3), 103.0 (6-CH), 109.3 (3-CH), 130.7, 144.8, 149.3, 150.5 (all C); HRMS (API$^+$) m/z [M + H]$^+$, $C_{13}H_{19}N_2O_4$ calcd. 267.1345, observed 267.1345.

Alternatively, 2,5-Dinitrobenzene **1b** (0.200 g, 0.9 mmol) and piperidine (0.35 ml, 3.6 mmol) were stirred at reflux for 2 h. EtOAc (20 ml) was added to the cool red residue, which was washed with brine (3 x 30 ml). The organic layer was dried ($MgSO_4$) and evaporated to dryness. The residue was purified by DCVC using gradient elution of EtOAc/hexane to give the title compound **2b** (0.182 g, 76%) as a yellow solid (spectroscopic data identical to above).

3.3. Synthesis of 1-(2,5-dimethoxy-4-nitrophenyl)pyrrolidine (3b)

2,5-Dinitrobenzene **1b** (0.286 g, 1.3 mmol) and pyrrolidine (0.42 ml, 5.0 mmol) were stirred at reflux for 2 h. EtOAc (20 ml) was added to the cool brown residue, which was washed with brine (3 x 30 ml). The organic layer was dried ($MgSO_4$) and evaporated to dryness to give the title compound **3b** (0.268 g, 82%), as an orange solid; mp 104–106 °C; R_f 0.45 (2 : 3 EtOAc : hexane); ν_{max} (neat, cm^{-1}) 2966 (w), 1608 (m), 1565 (m), 1526 (s), 1482 (m), 1450 (m), 1367 (w), 1287 (s), 1268 (s), 1218 (s); δ_H (400 MHz, $CDCl_3$) 1.91-1.95 (m, 4H, 2′-CH_2), 3.54-3.57 (m, 4H, 1′-CH_2), 3.74 (s, 3H, CH_3), 3.89 (s, 3H, CH_3), 5.96 (s, 1H, 6-H), 7.53 (s, 1H, 3-H); δ_C (100 MHz, $CDCl_3$) 25.5 (2′-CH_2), 50.8 (1′-CH_2), 56.6 (2 x CH_3), 97.1 (6-CH), 110.2 (3-CH), 126.1, 141.3, 146.1, 152.4 (all C); HRMS (API$^+$) m/z [M + H]$^+$, $C_{12}H_{17}N_2O_4$ calcd. 253.1188, observed 253.1187.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1: IR, ^{1}H, ^{13}C NMR spectra and HRMS for compounds **2b** and **3b**, and 2D NMR correlation spectra for **2b**.

Author Contributions: Methodology: T.M.S., M.R.A., I.B., and M.M. Conceptualization, Supervision, Writing – review & editing: F.A. All authors have read and approved the manuscript.

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

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