Short Note

N-(3,6-dimethoxy-2-nitrophenyl)acetamide

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N-(3,6-dimethoxy-2-nitrophenyl)acetamide

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Abstract

1,4-Dimethoxy-2,3-dinitrobenzene (**1**) reduction using sodium hydrosulfite gave 3,6-dimethoxybenzene-1,2-diamine (**2**) and 3,6-dimethoxy-2-nitroaniline (**3**) in 24% and 59% yield respectively. The nitroaniline **3** was acetylated with acetyl chloride to give *N*-(3,6-dimethoxy-2-nitrophenyl)acetamide (**4**) in 65% yield and with acetic anhydride to give *N*,*N*′-(3,6-dimethoxy-2-nitrophenyl)diacetamide (**5**) in 78% yield. Novel compounds **4** and **5** were characterized by FT-IR, ^{1}H and ^{13}C-NMR, and HRMS. The X-ray crystal structure of acetamide **4** is presented.

Keywords: aniline; benzoquinone; nitrobenzene; reduction; sodium dithionate

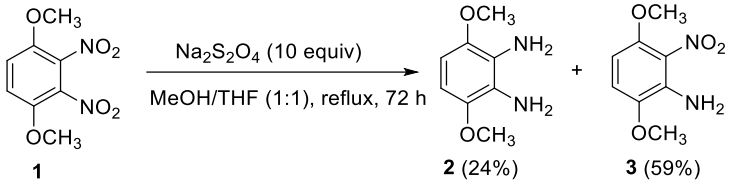
1. Introduction

1,4-Dimethoxy-2,3-dinitrobenzene (**1**) is privileged as a precursor for electro-reducible *para*-benzoquinones [1–3], including benzimidazolequinones [4–7], and quinoxalinediones [8], with potent anti-cancer and anti-microbial activities. The first transformative step towards *para*-benzoquinone targets is reduction to 3,6-dimethoxybenzene-1,2-diamine (**2**), which occurs in high yields using hydrogenation with Pd catalysis [1,8,9], and Sn in HCl [4–6,10].

2. Results and Discussion

2.1. Synthesis

Herein, dinitrobenzene **1** was reduced with sodium hydrosulfite (also known as sodium dithionate, $Na_2S_2O_4$) to give diamine **2** in 24% yield, and an unexpected adduct of incomplete reduction, 3,6-dimethoxy-2-nitroaniline (**3**) in 59% yield (Scheme 1).



Scheme 1. Reduction of 1,4-dimethoxy-2,3-dinitrobenzene (**1**) using sodium dithionate.

Acetylation of **3**, was inspired by recent exploitation of 2-nitroacetanilides as substrates for the synthesis of benzimidazoles [11,12]. Novel compound, *N*-(3,6-dimethoxy-2-nitrophenyl)acetamide (**4**) was prepared in 65% yield using acetyl chloride and triethylamine (Scheme 2). The 2-nitroacetanilide **4** in $CDCl_3$ exhibited broadening of the acetamide-methyl signal to give diminutive singlet peaks at 2.13 and 23.2 ppm in the respective ^{1}H and ^{13}C NMR spectra (Figures S1 and S2),

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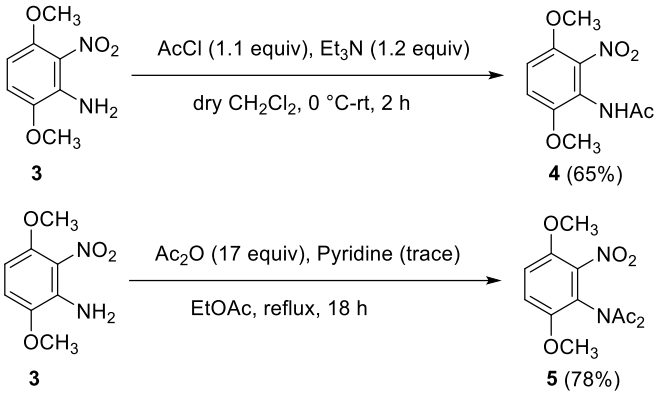
presumably due to amide-iminol tautomerism [13]. This is exacerbated by the adjacent nitro-group increasing the acidity of the N-H in **4**. Tautomerism was eliminated by preparation of the novel diacetamide **5** in 78% yield using acetic anhydride and catalytic pyridine (Scheme 2). For *N,N′*-(3,6-dimethoxy-2-nitrophenyl)diacetamide (**5**) in $CDCl_3$ the acetamide-methyl at 2.28 and 25.7 ppm in the respective ^{1}H and ^{13}C NMR spectra, appeared as one sharp singlet peak (Figures S3 and S4).



Scheme 2. Synthesis of *N*-(3,6-dimethoxy-2-nitrophenyl)acetamide (**4**) and *N,N′*-(3,6-dimethoxy-2-nitrophenyl)diacetamide (**5**).

2.2. X-Ray Crystallography

Recrystallization of *N*-(3,6-dimethoxy-2-nitrophenyl)acetamide (**4**) from chloroform in the NMR tube gave two polymorphs of compound (**4**), both of which were observable by optical microscopy (Figure S11). Crystals of each form were analyzed by single/crystal X-ray diffraction (SXD) crystallography to confirm molecular structure and tautomer (Figure 1).

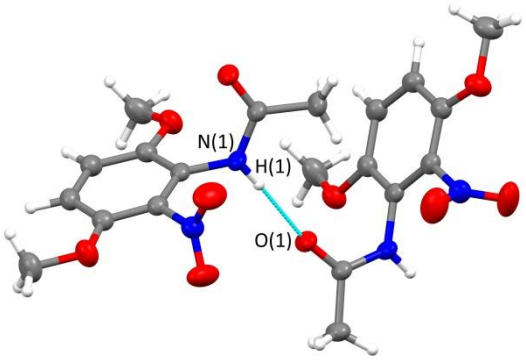


Figure 1. Molecular structure of *N*-(3,6-dimethoxy-2-nitrophenyl)acetamide (**4**) determined by SXD showing the hydrogen bond (N(1)—H(1)…O(1)) between two molecules in form I.

The thermodynamic form I with a single conformer of (**4**) has a monoclinic crystal structure with the positions of all H atoms unambiguously determined (Tables S1a-1e, Figure S14). In the solid state, only the amide tautomer (as opposed to iminol or aminol tautomers) is observed. The kinetic form II exhibits two conformers in the triclinic crystal structure with the positions of all non-methyl group H atoms equally determined and refined as for form I (Tables S2a-2e, Figure S15). Both conformers in form II are amide tautomers, the difference between them being in the torsion angles formed by the nitro and amide groups with the phenyl ring. Polymorphism of (**4**) results from multiple conformations of these two groups (Figure S16), and not from any molecular disorder. In both polymorphs, hydrogen bonding leads to a 1-dimensional network (Figure S17).

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3. Materials and Methods

3.1. Materials and Measurements

All chemicals were sourced from commercial suppliers and used without purification, including sodium hydrosulfite ($Na_2S_2O_4$, CAS Number: 7775-14-6, ≥82.5%, Sigma-Aldrich), $NaHCO_3$ (99%, EMSURE®, Supelco), acetyl chloride (AcCl, 98%, Sigma-Aldrich), triethylamine (Et_3N, ≥99.5%, Sigma-Aldrich), acetic anhydride (Ac_2O, 99.5%, Sigma-Aldrich), and pyridine (ACS reagent, ≥99%, Merck). HCl (37%, Fisher Scientific), NH_4OH (ammonia solution, 35%, Fisher Scientific), $CHCl_3$ (>99.8%, Fisher Scientific), ethyl acetate (EtOAc, ≥99%, Fisher Scientific), hexane (Fischer Scientific, bp 40–60 °C), methanol (MeOH, 99.9%, VWR Chemicals), and tetrahydrofuran (THF, ≥99%, Fisher Scientific), were used as received. Water is Milli-Q deionised and CH_2Cl_2 (>99.8%, Fisher Scientific) was freshly distilled over P_2O_5 (+99%, ACROS Organics). 1,4-Dimethoxy-2,3-dinitrobenzene (**1**) was prepared by reaction of nitric acid (69%, EMSURE®, Merck) with 1,4-dimethoxybenzene (ReagentPlus® 99%, Sigma-Aldrich), according to the literature procedure [1]. Thin layer chromatography (TLC) was performed on Merck TLC silica gel 60 F254 plates using a UV lamp (254 nm) for visualization. Column chromatography was performed using Fluka silica gel 60 (particle size 35–70 μm) using gradient elution of EtOAc and hexanes as eluent. The organic extract was dried using $MgSO_4$ (anhydrous, Extra Pure, Fisher Scientific). 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+. Apart for compound **3**, which was analysed using Bruker Avance NEO 600 MHz spectrometer with broadband autotune probe. NMR spectra were processed using TopSpin 3.3.0 acquisition software. NMR tubes used were 5 mm, Ultrathin Wall Precision NMR Sample Tubes 7″ L, 600 MHz, (545-PPT-7), from GPE-Scientific (Leighton Buzzard, Bedfordshire, UK). ^{13}C NMR spectra were acquired at 100 MHz using the 400 MHz spectrometer with complete proton decoupling. HRMS spectra of compounds **4** and **5** 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 accurate mass measurements has a tolerance of 6 and 5 ppm for compounds **4** and **5**, respectively.

*3.2. Synthesis of 3,6-Dimethoxy-2-nitroaniline (**3**)*

Sodium hydrosulfite (45.30 g, 0.26 mol) was added in three equal portions over 45 min to dintrobenzene **1** (6.00 g, 26 mmol) in MeOH/THF (1:1, 200 mL) at reflux. The stirred mixture was heated at reflux for 72 h. Water was added and the organic solvents evaporated, and the aqueous mixture acidified with conc. HCl (50 mL). The mixture was filtered and basified with conc. NH_4OH until pH 9. The solution was extracted with $CHCl_3$ (4 x 200 mL), the combined organic extracts dried ($MgSO_4$) and evaporated to dryness. The orange-brown residue was purified by column chromatography on silica gel using gradient elution of hexane and EtOAc to yield the *title compound* (3.03 g, 59%), as orange crystals; mp 77-78 °C (mp 76-77 °C) [14]; R_f 0.65 (1:4 hexane:EtOAc:); δ_H (600 MHz, $CDCl_3$) 3.84 (s, 3H, Me), 3.85 (s, 3H, Me), 5.39 (bs, 2H, NH_2), 6.18 (d, J = 8.8 Hz, 1H), 6.76 (d, J = 8.8 Hz, 1H); δ_C (100 MHz, CDCl3) 56.5, 56.8 (both Me), 98.4, 112.8 (both CH), 127.5, 135.2, 141.7, 148.6 (all C), and 3,6-dimethoxybenzene-1,2-diamine (**2**) (1.03 g, 24%), mp 87-89 °C (mp 86-87 °C) [1]; R_f 0.55 (1:4 hexane:EtOAc).

*3.3. Synthesis of N-(3,6-Dimethoxy-2-nitrophenyl)acetamide (**4**)*

AcCl (0.25 mL, 3.5 mmol) was added over 5 min to nitroaniline **3** (0.65 g, 3.3 mmol) and Et_3N (0.54 mL, 3.9 mmol) in dried CH_2Cl_2 (20 mL) at 0 °C and stirred at room temperature for 2 h. The solution was evaporated, EtOAc (50 mL) added, and washed with water (50 mL). The organic extract was dried ($MgSO_4$) evaporated to dryness, and purified by column chromatography on silica gel

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using gradient elution of hexane and EtOAc to yield the *title compound* (0.52 g, 65%), as yellow crystals; mp 167-170 °C; R_f 0.48 (EtOAc); ν_{max} (neat, cm^{-1}) 3169 (w), 2944 (w) 2842 (w), 1663 (C=O, m), 1590 (w), 1527 (NO_2, m), 1503 (m), 1466 (w) 1434 (w), 1368 (NO_2, m), 1261 (s), 1181 (w), 1098 (m), 1058 (m), 976 (w), 904 (s); δ_H (400 MHz, $CDCl_3$) 2.13 (bs, 3H), 3.85 (s, 6H), 6.89 (d, J = 9.2 Hz, 1H), 7.00 (d, J = 9.2 Hz, 1H), 7.14 (bs, 1H, N-H); δ_C (100 MHz, $CDCl_3$) 23.2, 56.7, 57.1 (all Me), 110.8, 113.7, 120.0, 127.7, 145.7, 147.3, 168.6 (C=O). HRMS (API^+) m/z $[M]^+$, $C_{10}H_{13}N_2O_5$ calcd. 241.0824, observed 241.0827.

*3.4. Synthesis of N,N′-(3,6-Dimethoxy-2-nitrophenyl)diacetamide (**5**)*

Ac_2O (4 mL, 42 mmol) and pyridine (3 drops) were added to nitroaniline **3** (0.50 g, 2.5 mmol) in EtOAc (5 mL) and stirred at reflux for 18 h. $CHCl_3$ (25 mL) was added and the organic layer washed with 1 M HCl (2 x 25 mL), dilute $NaHCO_3$ (3 x 25 mL), and water (25 mL). The organic extract was dried ($MgSO_4$) and evaporated to dryness to yield the *title compound* (0.55 g, 78%) as a yellow solid; mp 139-140 °C; R_f 0.65 (1:1 EtOAc:hexane); ν_{max} (neat, cm^{-1}) 1731 (m, C=O), 1710 (s, C=O), 1545 (NO_2, m), 1496 (s), 1457 (m), 1417 (w), 1364 (NO_2, s), 1270 (s), 1220 (s), 1206 (s), 1185 (s), 1164 (w), 1107 (m), 1062 (s), 1021 (s); δ_H (400 MHz, $CDCl_3$) 2.28 (s, 6H), 3.83 (s, 3H), 3.87 (s, 3H), 7.09 (AB-q, J = 9.3 Hz, 2H); δ_C (100 MHz, $CDCl_3$) 25.7 (2 x Me), 56.7, 57.0 (both OMe), 114.3, 114.5 (both CH), 121.5, 139.9, 145.2, 149.2 (all C), 171.9 (2 x C=O); HRMS (API^+) m/z $[M + H]^+$, $C_{12}H_{15}N_2O_6$ calcd. 283.0930, observed 283.0929.

*3.5. X-Ray Crystallography of N-(3,6-Dimethoxy-2-nitro-phenyl)acetamide (**4**)*

Crystal structures for two polymorphs of compound (**4**) were determined by laboratory single-crystal X-ray diffraction. Full experiment details and crystallographic tables are available in the supporting information.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, File S1: ^1H, and ^{13}C NMR spectra for compounds **3**-**5**, HRMS and FT-IR spectra for compounds **4** and **5**, and crystallographic data for compound **4**.

Author Contributions: Investigation: L.A.A.; Investigation (X-ray) and Writing: J.C.B. and J.K.C.; Supervision: G.T.; Conceptualization, Supervision, Writing—review & editing: F.A. All authors have read and approved the manuscript.

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Data Availability Statement: CIF files have been deposited at the Cambridge Crystallographic Data Centre (CCDC) with deposition numbers: 2531842-3. The data are contained within this article and its Supplementary Materials.

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

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