Short Note

2,2'-(1,4-Phenylene)bis(7-nitro-1*H*-benzimidazole 3-oxide)

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Abstract: Bis(benzimidazol-2-yl-3-oxide)benzene derivatives have potential applications as energetic or photoactive materials. By using a two-step one-pot approach employing microwave heating as a tool, 2,2'-(1,4-phenylene)bis(7-nitro-1*H*-benzimidazole 3-oxide) (**1**) has been prepared in 94% yield. In the first step an S_NAr reaction is performed using *p*-xylylenediamine as the central building block. Without isolating the intermediate, a base-mediated cyclization reaction follows in the second step. The product was isolated in analytically pure form by means of a pH-controlled precipitation.

Keywords: benzimidazole; benzimidazole *N*-oxide; microwave heating; two-step one-pot; precipitation

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1. Introduction

Heterocyclic compounds play a central role in a range of applications, such as drug development and materials chemistry [1–4]. Benzimidazoles and benzimidazole *N*-oxides fall into this category (Figure 1a) [5,6]. Despite the potential applicability of these compounds, there are surprisingly few synthetic routes reported for their preparation. The synthesis of benzimidazole *N*-oxides is usually carried by means of a base-mediated cyclization reaction of suitably-functionalized *o*-nitroanilines instead of direct oxidation of benzimidazoles [7]. One approach involves a two-step process [8–10]. In the first step, 2-nitroanilines are prepared by an S_NAr reaction between a haloarene and an amine. This is followed by a cyclization. Using this route, we have developed both batch microwave-heated and conventionally-heated continuous-flow protocols (Figure 1b) [11,12]. Using our methodologies, we have prepared a library of over 40 benzimidazole-*N*-oxides. We have also probed the mechanism of the reaction [13].

While simple heterocycles have application, an area of increasing interest is the preparation and application of fused heterocyclic compounds. These are finding particular value as energetic or photoactive materials [14–18]. Polycyclic benzimidazoles have interesting photochemical properties [19] as well as behaving as exhibiting remarkable anion transport activity [20]. In light of this, we decided to test the effectiveness of our methodology in the preparation of bis(benzimidazol-2-yl-3-oxide)benzene derivatives (Figure 1c). We have been successful in this endeavor and report our first example here.

(a) Benzimidazole and benzimidazole-*N*-oxide scaffolds **(b) Two-step one-pot approach to the preparation of benzimidazole-*N*-oxides** **(c) Bis(benzimidazol-2-yl-3-oxide)benzene scaffold**

Figure 1. (a) The benzimidazole and benzimidazole-*N*-oxide scaffolds; (b) a two-step one-pot approach to the preparation of benzimidazole-*N*-oxides; (c) bis(benzimidazol-2-yl-3-oxide)benzene scaffold.

2. Results

Our objective for preparing a bis(benzimidazol-2-yl-3-oxide)benzene derivative was to build on our previously reported two-step route [12]. We wanted to use ethanol as the solvent for the S_NAr reaction between *p*-xylylenediamine and 2-chloro-1,3-dinitrobenzene. We then planned to perform a bis-cyclization in basic aqueous media without isolation of the diamine intermediate. The overall reaction pathway to our target compound, 2,2'-(1,4-phenylene)bis(7-nitro-1*H*-benzimidazole 3-oxide) (**1**) is shown in Scheme 1. We planned to use microwave heating as a tool for both steps. In step one, we placed a 1:2 stoichiometric ratio of *p*-xylylenediamine, 2-chloro-1,3-dinitrobenzene, along with triethylamine and ethanol in a glass tube. The tube was sealed with a septum and placed into a scientific microwave unit and the contents heated at 120 °C for 20 min, stirring constantly. After allowing the mixture to cool to below 50 °C, we removed the vessel from the microwave cavity and added 0.5 M aqueous potassium carbonate (2 mL) before heating the reaction mixture at 120 °C for a further 20 min. Our main focus then became isolation of the product in pure form. To achieve this, we acidified the crude product mixture to a pH of between 3.5 and 5 at which point a significant amount of a dark orange solid precipitated from the solution. Placing the reaction vessel in an ice bath resulted in further precipitation of the product. Filtration and drying of the orange solid gave us the desired product, **1**, in 94% yield and in analytically pure form. Mechanistically, the reaction proceeds by the pathway we have reported previously for the preparation of monomeric analogs [10,13]. We characterized **1** by NMR and IR spectroscopy, UV-vis spectrophotometry, and high-resolution mass spectrometry. The 1H -NMR spectrum (Supplementary Materials) shows a broad peak at 12.83 ppm (2H) for the NH group, a singlet at 8.57 ppm (4H) corresponding the equivalent protons of the central phenyl ring, and then the coupled peaks corresponding to the nitro-benzimidazole moieties: 8.14 ppm (dd, $J = 8.1, 1.0$ Hz, 2H), 8.04 ppm (dd, $J = 8.0, 1.0$ Hz, 2H), and 7.52 ppm (t, $J = 8.0$ Hz, 2H). This assignment was also supported by a 2D-NMR HSQC experiment. The IR spectrum shows a characteristic peak for the N–O

vibration of *N*-oxides [8] at 1249 cm^{-1} and peaks attributable to the nitro group [21] at 1513 and 1327 cm^{-1} .

Scheme 1. Preparation of 2,2'-(1,4-phenylene)bis(7-nitro-1*H*-benzimidazole 3-oxide) (**1**).

3. Materials and Methods

3.1. General

All reactions were performed using a CEM Discover SP microwave unit, in closed vessel configuration. Temperature was measured by means of an IR temperature sensor. NMR spectra (^1H , ^{13}C) were recorded at 300 K using a Bruker DRX-400 400 MHz spectrometer. The ^1H -NMR spectrum was referenced to residual non-deuterated dimethylsulfoxide (2.50 ppm) in $\text{DMSO-}d_6$ and the ^{13}C -NMR spectrum was referenced to DMSO (39.52 ppm). The high-resolution mass spectrum was collected on an Applied Biosystems QSTAR Elite instrument equipped with an electrospray ionization (ESI) source, calibrated using Agilent LC/MS tuning mix. The IR spectrum was recorded from neat material on a Bruker Alpha FTIR spectrometer using an attenuated total reflection (ATR) diamond crystal. The UV-Vis data was obtained in DMF using a Varian Cary 100 spectrophotometer.

3.2. Chemicals

Deuterated dimethyl sulfoxide (d_6 -DMSO) was purchased from Cambridge Isotope Laboratories (Tewksbury, MA, USA). 2-Chloro-1,3-dinitrobenzene [CAS 606-21-3] was purchased from Alfa Aesar. *p*-Xylylenediamine [CAS 539-48-0] was purchased from TCI (Portland, OR, USA). Triethylamine [CAS 121-44-8] was purchased from Fisher Scientific (Fair Lawn, NJ, USA). Ethanol [CAS 4-17-5] was obtained from Pharmaco-Aaper (Brookfield, CT, USA). Potassium carbonate [CAS 584-08-7] was purchased from J. T. Baker (Center Valley, PA, USA).

Preparation of 2,2'-(1,4-phenylene)bis(7-nitro-1*H*-benzimidazole 3-oxide) (1**).** To a 10 mL-capacity glass tube equipped with a magnetic stir bar was added 2-chloro-1,3-dinitrobenzene (0.12 g, 0.6 mmol, 2 eq), *p*-xylylenediamine (0.041 g, 0.3 mmol, 1 eq), triethylamine (0.06 g, 0.6 mmol, 2 eq), and ethanol (3 mL). The reaction vessel was sealed with a septum and placed into the microwave cavity. Stirring throughout, the contents of the vessel was heated to $120\text{ }^\circ\text{C}$ using an initial microwave power of 100 W and held at this temperature for 20 min; the microwave power automatically fluctuated to hold the reaction mixture at the desired temperature. After the allotted time, the contents of the reaction vessel was allowed to cool to below $50\text{ }^\circ\text{C}$ before taking the vessel out of the microwave unit. The septum was removed, 0.5 M aqueous potassium carbonate (2 mL) added, and the septum then replaced. The vessel was then replaced into the microwave unit and heated at $120\text{ }^\circ\text{C}$

for 20 min using an identical protocol to that for the first step of the reaction. After cooling, removing from the microwave unit, and de-capping, the product mixture was transferred to a beaker and diluted by the addition of water (10 mL). Some precipitation of an orange solid was observed at this point. The product mixture was acidified with 2M hydrochloric acid to a pH of between 3.5 and 5 at which point a significant amount of dark orange solid precipitated from the solution. The beaker was placed into an ice bath for 1 h to promote further product precipitation. After this time, the solid product was removed by filtration and dried at 60 °C. Analytically pure 2,2'-(1,4-phenylene)bis(7-nitro-1H-benzimidazole 3-oxide) (**1**) was obtained as a dark orange solid (121.7 mg, 94%). ¹H-NMR (400 MHz, DMSO-*d*₆) δ 12.83 (br s, 2H, NH), 8.57 (s, 4H), 8.14 (dd, *J* = 8.1, 1.0 Hz, 2H), 8.04 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.52 (t, *J* = 8.0 Hz, 2H). ¹³C-NMR (101 MHz, DMSO) δ 149.20, 138.24, 136.30, 131.37, 129.63, 128.95, 122.47, 119.48, 116.43. HRMS (ESI) *m/z* calculated for C₂₀H₁₃N₆O₆ [M+H]⁺ 433.0897, found 433.0910. IR ν/cm^{−1} 1513 (NO₂), 1444, 1327 (NO₂), 1246 (N–O), 731. UV-vis (DMF) λ_{max} = 395 nm (ε/dm³ mol^{−1} cm^{−1} = 31,360).

4. Conclusions

A bis(benzimidazol-2-yl-3-oxide)benzene derivative has been prepared rapidly and in 94% isolated yield by means of a two-step one-pot approach using microwave heating as a tool. In the first step an S_NAr reaction is performed using *p*-xylylenediamine as the central building block. A base-mediated cyclization reaction follows in the second step. The product could be isolated in analytically pure form by means of a pH-controlled precipitation.

Supplementary Materials: The following are available online: Copies of the ¹H- and ¹³C-NMR, IR, UV, and high-resolution spectra.

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References

1. Meanwell, N.A.; Lolli, M.L. (Eds.) *Applications of Heterocycles in the Design of Drugs and Agricultural Products*; Elsevier: Oxford, UK, 2021.
2. Li, J. (Ed.) *Heterocyclic Chemistry in Drug Discovery*; John Wiley and Sons Inc.: Hoboken, NJ, USA, 2013.
3. Smith, C.A.; Narouz, M.R.; Lummis, P.A.; Singh, I.; Nazemi, A.; Li, C.-H.; Crudden, C.M. N-Heterocyclic Carbenes in Materials Chemistry. *Chem. Rev.* **2019**, *119*, 4986–5056. [[CrossRef](#)] [[PubMed](#)]
4. Mlostoń, G. Heterocycles in Materials Chemistry. *Chem. Heterocycl. Compd.* **2017**, *53*, 1. [[CrossRef](#)]
5. Tahlan, S.; Kumar, S.; Narasimhan, B. Pharmacological Significance of Heterocyclic 1H-Benzimidazole Scaffolds: A Review. *BMC Chem.* **2019**, *13*, 101. [[CrossRef](#)] [[PubMed](#)]
6. Prajapat, P.; Kumawat, M.; Talesara, G.L.; Kalal, P.; Agarwal, S.; Kapoor, C.S. Benzimidazole Scaffold as a Versatile Biophore in Drug Discovery: A Review. *Chem. Biol. Interface* **2018**, *8*, 1–10.
7. Nikitina, P.A.; Perevalov, V.P. Methods of synthesis and physicochemical properties of 1-hydroxyimidazoles, imidazole 3-oxides, and their benzoannulated analogs. *Chem. Heterocycl. Compd.* **2017**, *53*, 123–149. [[CrossRef](#)]
8. Buján de Vargas, E.I.; Cañas, A.I. From *N*-n-butyl-2,6-dinitroaniline to a Fused Heterocyclic *N*-oxide. *Tetrahedron Lett.* **1996**, *37*, 767–770. [[CrossRef](#)]
9. Buján, E.I.; Salum, M.L. A simple synthesis of benzimidazole *N*-oxides from 2-nitroaniline derivatives—Scope and limitations. *Can. J. Chem.* **2004**, *82*, 1322–1327. [[CrossRef](#)]
10. Buján, E.I.; Salum, M.L. From *N*-(dinitrophenyl) amino acids to benzimidazole *N*-oxides. Synthesis, kinetics and mechanism. *J. Phys. Org. Chem.* **2006**, *19*, 187–195.
11. Politano, F.; Buján, E.I.; Leadbeater, N.E. Preparation of benzimidazole *N*-oxides by a two-step continuous flow process. *Chem. Heterocycl. Compd.* **2016**, *52*, 952–957. [[CrossRef](#)]

12. Politano, F.; Gran-Magano, A.K.; Leadbeater, N.E. One-Pot Two-Step Synthesis of 2-Aryl benzimidazole *N*-oxides Using Microwave Heating as a Tool. *Molecules* **2019**, *24*, 3639. [[CrossRef](#)] [[PubMed](#)]
13. Politano, F.; Sandoval, A.L.; Uranga, J.G.; Buján, E.I.; Leadbeater, N.E. Using Experimental and Computational Approaches to Probe an Unusual Carbon-Carbon Bond Cleavage Observed in the Synthesis of Benzimidazole *N*-Oxides. *Org. Biomol. Chem.* **2021**, *19*, 208–215. [[CrossRef](#)] [[PubMed](#)]
14. Gao, H.; Zhang, Q.; Shreeve, J.M. Fused Heterocycle-Based Energetic Materials (2012–2019). *J. Mater. Chem. A* **2020**, *8*, 4193–4216. [[CrossRef](#)]
15. Wu, J.-T.; Xu, J.; Li, W.; Li, H.-B. Coplanar Fused Heterocycle-Based Energetic Materials. *Propellants Explos. Pyrotech.* **2020**, *45*, 536–545. [[CrossRef](#)]
16. Tsyshevsky, R.; Smirnov, A.S.; Kuklja, M.M. Comprehensive End-To-End Design of Novel High Energy Density Materials: III. Fused Heterocyclic Energetic Compounds. *J. Phys. Chem. C* **2019**, *123*, 8688–8698.
17. Nitha, P.R.; Soman, S.; John, J. Indole Fused Heterocycles as Sensitizers in Dye-Sensitized Solar Cells: An Overview. *Mater. Adv.* **2021**, *2*, 6136–6168. [[CrossRef](#)]
18. Makhova, N.N.; Belen'kii, L.I.; Gazieva, G.A.; Dalinger, I.L.; Konstantinova, L.S.; Kuznetsov, V.V.; Kravchenko, A.N.; Krayushkin, M.M.; Rakitin, O.A.; Starosotnikov, A.M.; et al. Progress in the Chemistry of Nitrogen-, Oxygen- and Sulfur-Containing Heterocyclic Systems. *Russ. Chem. Rev.* **2020**, *89*, 55–124. [[CrossRef](#)]
19. Manna, S.K.; Das, T.; Samanta, S. Polycyclic Benzimidazole: Synthesis and Photophysical Properties. *ChemistrySelect* **2019**, *4*, 8781–8790. [[CrossRef](#)]
20. Peng, C.-C.; Zhang, M.-J.; Sun, X.-X.; Cai, X.-J.; Chen, Y.; Chen, W.-H. Highly Efficient Anion Transport Mediated by 1,3-Bis(benzimidazol-2-yl)benzene Derivatives Bearing Electron-Withdrawing Substituents. *Org. Biomol. Chem.* **2016**, *14*, 8232–8236. [[CrossRef](#)] [[PubMed](#)]
21. Annor-Gyamfi, J.K.; Gnanasekaran, K.K.; Bunce, R.A. Syntheses of 1-Aryl-5-nitro-1*H*-indazoles and a General One-Pot Route to 1-Aryl-1*H*-indazoles. *Molecules* **2018**, *23*, 674. [[CrossRef](#)] [[PubMed](#)]