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An improved synthesis, characterization, and X-ray studies of 5-*tert*-butyl-3-nitrophthalonitrile

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ABSTRACT

An improved six-step synthesis of 5-*tert*-butyl-3-nitrophthalonitrile (**1**) is described. The title compound and all the intermediates are fully characterized spectroscopically (FT–IR, ^{1}H NMR, ^{13}C NMR, MS). In addition, single-crystal X-ray diffraction further confirmed the structure of the title compound.

Phthalocyanines are an important industrial commodity with a wide range of applications. They can be prepared from aromatic *ortho*-disubstituted derivatives including *o*-cyanobenzamides, phthalic acids, phthalic anhydrides, phthalimides, phthalamides, 1,3-diiminoisoindolines, and phthalonitriles.[1] The most useful of all the phthalocyanine precursors are phthalonitriles.[2] Heating of phthalonitriles in high boiling solvents in the presence of metal salts results in templated cyclotetramerization and formation of a phthalocyanine dye. Unsubstituted and some simple substituted phthalonitriles are available from commercial sources, but the vast majority need to be synthesized, often via multi-step, challenging routes.

Recently, as part of an ongoing project, we became interested in phthalocyanines with electron-donating/electron-accepting properties suitable for energy conversion applications. For this purpose we needed a precursor that would result in a phthalocyanine having bulky groups at the periphery of the molecule, thereby increasing its solubility while suppressing aggregation. We were also looking for a precursor possessing a functional group with electron donating/electron-accepting properties. After an extensive literature review we turned our attention to 5-*tert*-butyl-3-nitrophthalonitrile which possessed both properties, viz. the presence of both a bulky *tert*-butyl group and a nitro functionality (electron-withdrawing), which upon reduction to an amino group would provide the target phthalocyanine with electron-donating properties.

5-*tert*-Butyl-3-nitrophthalonitrile (**1**) was first reported in 1975 by Mikhalenko and Lukyanets,[3] who proposed a synthetic pathway starting from *ortho*-xylene, which after seven consecutive steps (alkylation, introduction of the nitro functionality, oxidation to phthalic acid, dehydration to the anhydride, conversion into the phthalimide, ammonolysis into the phthalamide, followed by dehydration to the phthalonitrile), resulted in formation of 5-*tert*-butyl-3-nitrophthalonitrile. Unfortunately, no spectral characterization of the final product or intermediates, that would corroborate the identity of the compounds, was provided. Moreover, it lacked experimental details, including reaction conditions, separation methods, and reaction yields. Thus, we decided to reinvestigate the synthesis of 5-*tert*-butyl-3-nitrophthalonitrile (**1**) as well as to provide full spectroscopic characterization of all the intermediates and X-ray characterization of the final product.

The subject of this paper is an improved synthesis and characterization of 5-*tert*-butyl-3-nitrophthalonitrile (**1**).

The synthesis of 5-*tert*-butyl-3-nitrophthalonitrile (**1**) is presented in Scheme 1. In the first step, the *tert*-butyl group was introduced to *ortho*-xylene (**2**) by a modification of a well-established Friedel–Crafts alkylation in a higher 85% yield than that previously reported.[4,5]

Regioselective nitration of 4-*tert*-butyl-*o*-xylene (**3**) was first described by Brundrett and White in 1974.[6] They claimed that 5-*tert*-butyl-3-nitro-*o*-xylene (**4a**) was obtained in a 60% yield. However, we failed to reproduce this protocol. Contrary to the report by Brundrett and White, we found that nitration of **3** resulted in a rather complex mixture of at least three derivatives, one of which was indeed 5-*tert*-butyl-3-nitro-*o*-xylene (**4a**) (48% yield). After arduous separation and detailed spectroscopic analysis, two other products were identified as 4-*tert*-butyl-3,6-dinitro-*o*-xylene (**4b**) (7% yield) and 5-*tert*-butyl-3,4-dinitro-*o*-xylene (**4c**) (10% yield) (Fig. 1).

Oxidation of the methyl groups in 5-*tert*-butyl-3-nitro-*o*-xylene (**4a**) with $KMnO_4$ in water/pyridine solution gave phthalic acid **5** in 74% yield. The IR spectrum of **5** was dominated by a sharp

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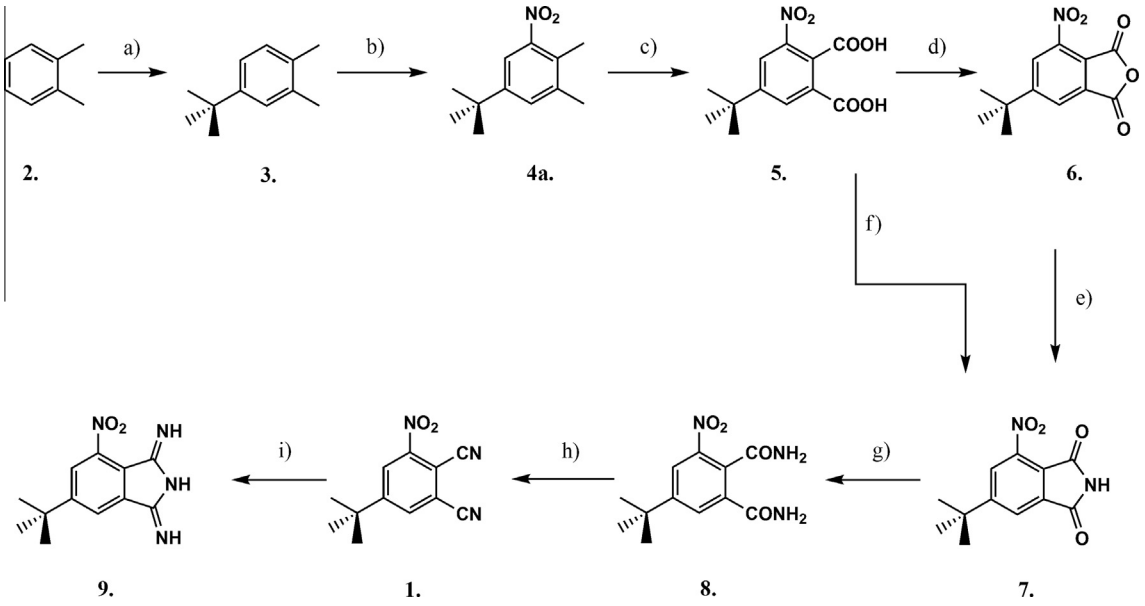

Scheme 1. Reagents and conditions: (a) $FeCl_3$, *t*-BuCl, 0 °C to rt, 24 h, 85%; (b) fuming HNO_3/conc. H_2SO_4, rt, 24 h, 48%; (c) $KMnO_4$, py/H_2O, 4 h, reflux, 74%; (d) AcCl, 2 h, reflux, 54%; (e) urea, 180 °C, 45 min, 88%; (f) formamide, 190 °C, 1 h, 78%; (g) NH_3, MeOH, rt, ca. 24 h, 73%; (h) $POCl_3$, py, 0 °C to rt, 1.5 h, 59%; (i) NH_3, MeOH, rt, quant.

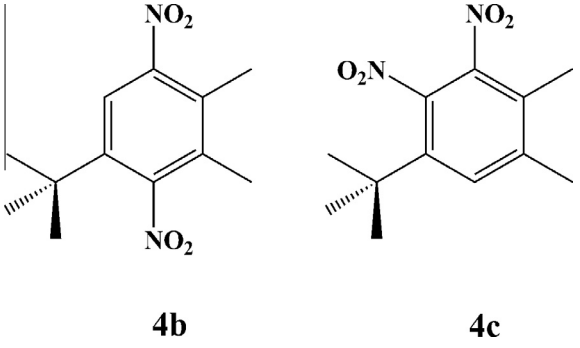

Figure 1. Structures of 4-*tert*-butyl-3,6-dinitro-*o*-xylene (**4b**) and 5-*tert*-butyl-3,4-dinitro-*o*-xylene (**4c**) isolated after nitration of 4-*tert*-butyl-*o*-xylene (**3**).

absorption band at 1701 cm^{-1} (C═O) and a broad band at 3417 cm^{-1} (–OH). Negative ion mode ESI-MS revealed a molecular ion peak at *m/z* 266 $[M-H^+]^-$.

The classic protocol used to obtain phthalonitriles requires that phthalic acids be converted into phthalic anhydrides. This was achieved by refluxing 5-*tert*-butyl-3-nitrophthalic acid (**5**) in acetyl chloride. Upon chromatographic separation, anhydride **5** was isolated in 54% yield. Two strong bands at 1799 cm^{-1} and 1735 cm^{-1} observed in the IR spectrum, along with the disappearance of the previously observed absorption band at 1701 cm^{-1} corroborated unambiguously the formation of cyclic anhydride **6**. It was however found that anhydride **6** had limited stability, and with time decomposed to phthalic acid **5**. Thus, it is important to consume the obtained phthalic anhydride **6** immediately after its formation. However, we found that the phthalic acid **5** could be directly converted into the phthalimide **7**, which allowed us to skip one reaction step, thereby simplifying the procedure and improving the total reaction yield. We applied the procedure first disclosed in a Japanese patent[7] and then successfully adopted by Hanack and Vagin.[8] Treatment of phthalic acid **5** at elevated temperature with formamide (190 °C) afforded phthalimide **7** in a good 78% yield. Simple extraction with dichloromethane was sufficient to obtain a product with good purity. A strong absorption in the IR spectrum at 3203 cm^{-1} indicated the presence of an N–H stretch, while two strong absorption bands at 1782 cm^{-1} and 1725 cm^{-1} were evidence of a C═O stretching vibration. The MALDI–TOF spectrum of phthalimide **7** was dominated by a peak at *m/z* 271.050 which was interpreted as the sodium adduct $[M+Na^+]^+$.

Treatment of phthalimide **7** with a saturated methanolic solution of ammonia, followed by chromatographic separation gave the corresponding phthalamide **8** in a satisfactory 73% yield. In the IR spectrum of **8** three bands at 3373 cm^{-1} (N–H), 3180 cm^{-1} (N–H), and 1660 cm^{-1} (C═O) were characteristic of primary amides.

Conversion of phthalamide **8** into the corresponding phthalonitrile **1** was carried out with phosphorus oxychloride as the dehydrating agent in dry pyridine.[9] Finally, after chromatographic separation, pure phthalonitrile **1** was obtained in 59% yield. The ^1H NMR spectral data, confirmed the assigned structure of **1**, both by the splitting pattern of the signals in the aromatic region (δ = 8.1 and 8.52 ppm, both seen as doublets with coupling constants of 1.87 Hz) and by integration of the signals observed for the alkyl and aromatic protons (9:2 ratio). The splitting of the aromatic proton signals was particularly valuable for identifying the substitution pattern of the aromatic ring. The coupling constants of 1.87 Hz clearly indicated that both protons were located at *ortho* and *para* positions with respect to the nitro group, and therefore the 1,2,3,5-substitution pattern was corroborated unambiguously. Due to the presence of the strong electron-withdrawing $-NO_2$ group attached to the aromatic ring, both aromatic protons experience deshielding, causing their signals to move downfield. In the IR spectrum a prominent band at 2236 cm^{-1} was characteristic of aromatic nitriles. In addition, a molecular ion peak at *m/z* 229 $[M^-]$ was observed in the ESI mass spectrum.

Slow evaporation of a saturated hexane solution of **1** resulted in crystals with good morphology, and the molecular structure of **1** was further determined by single crystal X-ray diffraction (Fig. 2). This revealed that the nitro group was indeed introduced regioselectively at position 3. Detailed crystallographic data such as bond lengths and angles are presented in the Supplementary Data. [10]

It is worth noting that phthalonitrile **1** could be easily transformed into its more reactive form, namely 1,3-diiminoisoindoline **9**. Diiminoisoindolines are the precursors of choice for the synthesis of metal-free, silicon and germanium phthalocyanines as well

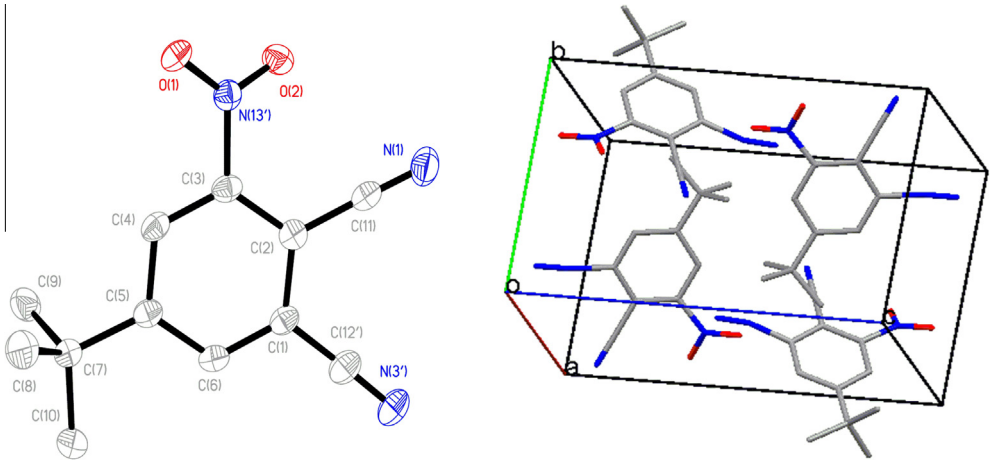

Figure 2. ORTEP plot of phthalonitrile **1** and the monoclinic unit cell representation with P21/c space group.

as in those cases where phthalocyanine complexes of less reactive metals are to be obtained.[2,11] The reaction was straightforward and simply involved reacting ammonia gas with a methanolic solution of **1** at room temperature (sodium methoxide as a catalyst was not needed). 1,3-Diiminoisoindoline **9** (as confirmed by ESI-MS, *m/z* 247 $[M+H]^+$) was obtained quantitatively.

In summary, we have investigated and improved the protocol for the synthesis of 5-*tert*-butyl-3-nitrophthalonitrile (**1**) starting from inexpensive and easily available *ortho*-xylene (**2**). Contrary to previous reports, it was found that nitration of 4-*tert*-butyl-*o*-xylene (**3**), gave a complex mixture of mono-nitro and di-nitro derivatives. This mixture, when separated into its individual components, constitutes a useful source of di-nitro derivatives of 4-*tert*-butylphthalonitrile, which represents a potentially useful building block for the synthesis of *nitro*-substituted phthalocyanines. By applying a direct transformation of phthalic acid **5** into phthalimide **7** we were able to skip one reaction step (i.e., the formation of phthalic anhydride) thus simplifying the entire protocol and improving the total yield of the target compound. The phthalonitrile under discussion was recently used in our laboratory to prepare a set of nitro- and amino-substituted phthalocyanines for solar energy conversion applications.[3]

Acknowledgements

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Supplementary data

Supplementary data (computational details and a list of atomic coordinates and their estimated standard deviations for 5-*tert*-butyl-3-nitrophthalonitrile (**1**). ^{1}H NMR, IR, and MS spectra of selected intermediates.) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.045.

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9. 5-*tert*-butyl-3-nitrophthalonitrile (**1**): 5-*tert*-butyl-3-nitrophthalamide (**8**) (2.63 g, 10 mmol) was dissolved in pyridine (dry, freshly distilled, 15 mL) and cooled to 0 °C, followed by slow addition of $POCl_3$ (4.6 g, 2.75 mL, 30 mmol). The mixture was kept at 0 °C for 0.5 h and then at room temperature for 1 h. After completion of the reaction, the mixture was poured onto ice and extracted with CH_2Cl_2. The organic layer was washed with H_2O three times. After evaporation of the solvent, the residue was chromatographed on silica gel (column length 20 cm). A mixture of toluene/hexane 2:1 was passed through the silica gel to remove impurities and then it was changed to toluene to elute the pure product (1.33 g, 59%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.43 (s, 9H), 8.1 (d, 1H, $^4J_{meta}$ 1.87 Hz), 8.52 (d, 1H, $^4J_{meta}$ 1.87 Hz). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 30.6, 36.3, 108.5, 111.8, 114.3, 119.4, 126.3, 135.2, 149.3, 159.9. GC–MS: *m/z* 229 M^+, 214 $[M-CH_3]^+$. ESI-MS (negative ion mode): *m/z* = 229 $[M^-]$, 199 $[M-NO^+]^-$. FT–IR (KBr): ν = 3080 (Ar–H), 2968 (*t*-Bu) m, 2912, 2874, 2236 (CN) s, 1609, 1556 (NO_2) s, 1544 (NO_2) s, 1479, 1464, 1402, 1368, 1350 (NO_2) s, 1282, 1246, 1217, 1176, 927, 805, 772, 762, 644, 548 cm^{-1}.
10. Crystallographic data for the structure in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 933174. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 0 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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