Tetrahedron Letters 54 (2013) 4388–4391

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis and spectroscopic properties of 5-*tert*-butyl-3-(trifluoromethyl)phthalonitrile: a novel precursor for the synthesis of phthalocyanines

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ARTICLE INFO

Article history:
Received 8 April 2013
Revised 16 May 2013
Accepted 30 May 2013
Available online 10 June 2013

Keywords:
Phthalonitriles
Electrophilic substitution
Nucleophilic trifluoromethylation
Phthalocyanines

ABSTRACT

The synthesis and spectroscopic characterization of the new phthalonitrile 5-*tert*-butyl-3-(trifluoromethyl)phthalonitrile is reported. A six-step route, which started with a regiospecific iodination, followed by CuI-catalyzed trifluoromethylation, is discussed. The title compound is also converted into the more reactive compound 6-*tert*-butyl-4-trifluoromethyl-1,3-diiminoisoindoline.

Fluorine-containing motifs, such as fluoro (F-), difluoromethyl (CHF_2-), and trifluoromethyl (CF_3-) groups, are present in the structures of many compounds which are important to the pharmaceutical and agricultural industry.[1] For example, a trifluoromethyl group attached to the aryl ring can be found in many commercially available medications, such as Prozac (antidepressant), Nexavar (anticancer), Naturetin (antihypertensive), Emeden (antiemetic), Viroptic (antiviral), Lariam (antimalarial), and Sensipar (calcimimetic).[2] Fluorine and fluorine-containing functional groups are introduced into biologically active compounds in order to improve their pharmacokinetic, pharmacodynamic, and physicochemical parameters, for example lipophilicity, stability, or blood circulation time.[3] It has become evident that appropriate positioning of the fluorine-containing group in a molecule can modify greatly its physicochemical properties, and its biological activity. The portfolio of commercially available fluorinating agents has expanded greatly, with many showing high chemoselectivity and regioselectivity. In addition, many ready-to-use fluorine-containing building blocks have been reported, which facilitate the synthesis of new biologically active compounds and drug discovery.[4]

The classes of biologically active compounds which have been modified by attaching a fluorine-containing group to the parent structure include hormones, vitamins, antibiotics, carbohydrates, and small-ring heterocycles. Another group of fluorine-bearing motifs which have attracted a great deal of attention over the past 20 years are photosensitizers, such as porphyrins, phthalocyanines, corroles, and chlorins.[5] Photosensitizers, due to their ability to transfer the energy acquired by absorption of light to molecules of oxygen resulting in the formation of highly cytotoxic reactive oxygen species (ROS), have proven to be useful tools in cancer diagnosis and in photodynamic cancer therapy (PDT). In one of our current projects, we developed an interest in phthalocyanines as PDT active agents. Phthalocyanines seem to be better suited, more than any other group of organic dyes, as perfect candidates as photosensitizers in PDT. This is mainly due to their intrinsic properties, viz. efficient absorption of light in the visible and IR region, high molar extinction coefficients, good photochemical stability, and above all, an ability to produce efficiently the reactive oxygen species (ROS). Phthalocyanines are typically prepared from aromatic *ortho*-disubstituted derivatives, such as phthalic acids, phthalimides, or 1,3-diiminoisoindolines.[6,7] However, by far the most versatile precursors for the synthesis of phthalocyanines continue to be substituted phthalonitriles.[8] Despite the fact that many phthalonitriles are available from commercial sources, the synthesis of phthalonitriles with more sophisticated substitution patterns is far from trivial and often involves multistep routes. Herein, we describe a six-step synthesis of a novel trifluoromethyl-containing phthalonitrile as an important building block for the synthesis of phthalocyanines with interesting optical and biological properties.

Scheme 1 illustrates the synthesis of the phthalonitrile under discussion. A *tert*-butyl group was introduced into *ortho*-xylene (**1**) by modification of a well-established Friedel–Crafts alkylation. After distillation under reduced pressure, *ortho*-xylene **1** was

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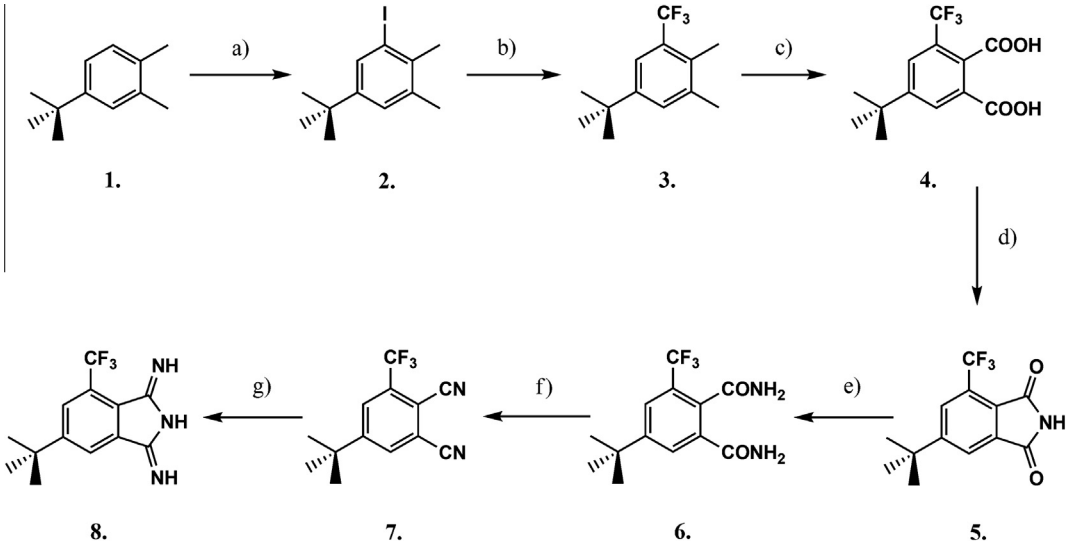
http://dx.doi.org/10.1016/j.tetlet.2013.05.145



Scheme 1. Reagents and conditions: (a) H_5IO_6, I_2, CH_3COOH, H_2SO_4, H_2O, 60–65 °C, 6 h, 81%; (b) CF_3COONa, CuI, NMP, 160 °C, 24 h, 41%; (c) $KMnO_4$, py/H_2O, 11 days, 100 °C, 96%; (d) formamide, 190 °C, 1 h, 96%; (e) NH_3, H_2O, MeOH, 80 °C, 1 h; (f) $POCl_3$, py, 0 °C to rt, 2 h, 23%; (g) MeOH, NH_3, NaOMe, rt, 24 h.

isolated in 85% yield.[9,10] Iodine was then introduced regiospecifically into **1** by a previously described route.[11]

The most synthetically useful method for the introduction of a trifluoromethyl (CF_3) group into an aromatic/heteroaromatic ring system is via coupling of the corresponding aryl/heteroaryl halide with a trifluoromethyl-copper species.[12] In this work, the trifluoromethyl group was introduced regiospecifically into **1** by utilizing sodium trifluoroacetate and copper(I) iodide in the dipolar aprotic solvent, NMP.[13,14] Care was taken to ensure strictly anhydrous reaction conditions to avoid reduction of the aromatic halide **2** into the corresponding aromatic hydrocarbon. It was found that the use of one equivalent of sodium trifluoroacetate and copper(I) iodide resulted in a 29% reaction yield, while the use of two equivalents of sodium trifluoroacetate and copper(I) iodide gave a 41% yield. Interestingly, a further increase in the amount of sodium trifluoroacetate and copper(I) iodide did not result in an improved reaction yield. The separation of the reaction product **3** from the unreacted substrate **2** proved to be a very arduous task. Three vacuum distillations were needed to obtain the product in sufficient purity (as judged by GC–MS). The regiospecific introduction of the CF_3 group to **2** was corroborated by mass spectrometry, IR, ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectroscopy. In the ^{13}C NMR spectrum the three fluorine atoms attached directly to the carbon atom resulted in a quartet centered at about 125 ppm with a coupling constant of ca. 274 Hz (see Supplementary data, Fig. S2). This large coupling constant is typical for direct one-bond coupling of the ^{19}F nucleus to a ^{13}C nucleus (^1J). Moreover, another quartet centered at around 128 ppm was discernible in the ^{13}C NMR spectrum with a coupling constant of 28 Hz, resulting from the coupling of the ^{19}F nucleus with the ^{13}C atom adjacent to the trifluoromethyl group. In this case, the coupling constant measured was defined as a two-bond coupling constant (^2J). Another quartet was evident at ca. 120 ppm with a coupling constant of 5.8 Hz. Here, the ^{19}F atoms of the trifluoromethyl group split the signal of the C-4 of the aromatic ring giving rise to the three-bond coupling (^3J).[15] In the ^{1}H NMR spectrum, two doublets were observed in the aromatic region of the spectrum with equal intensities and coupling constants of ca. 2.2 Hz (see Supplementary data, Fig. S1). The measured coupling constant clearly indicated that both aromatic protons were located in *meta* positions, thereby the 1,2,3,5-substitution pattern was unambiguously corroborated. Moreover, in the ^{19}F NMR spectrum a signal centered at –60.19 ppm confirmed the presence of the trifluoromethyl group (see Supplementary data, Fig. S3).

Oxidation of the methyl groups in **3** was carried out in order to obtain phthalic acid derivative **4**, which could be converted into a phthalonitrile **7** by a classical route (see Scheme 1). This was achieved by using $KMnO_4$ in water/pyridine mixture at 100 °C for 11 days. Compared to the other *ortho*-xylenes investigated in our laboratory, the oxidation of **3** proceeded very slowly and a very long reaction time was needed, phthalic acid **4** was eventually obtained in 95% yield. The IR spectrum of **4** was dominated by a sharp absorption band at 1699 cm^{-1} (C=O) and a broad absorption band spanning 3300 to 2500 cm^{-1} (–OH), while the ^{1}H NMR spectrum revealed a broad signal centered at 13.51 ppm accounting for the two protons of the carboxylic groups. The negative mode ESI mass spectrum revealed a peak at *m*/*z* 289 that was attributed to the $[M\text{-}H^+]^-$ ion (see Supplementary data, Figs. S6, S9 and S10).

In the next step, phthalic acid **4** was converted into phthalimide **5**. Simple heating of **4** in formamide at 190 °C for 1 h provided phthalimide **5** in a high 96% yield.[16,17] The product obtained was purified chromatographically using silica gel. A strong absorption in the IR spectrum at 3218 cm^{-1} indicated the presence of an N–H stretching vibration, while two strong absorption bands at 1776 cm^{-1} and 1722 cm^{-1} were assigned to C=O stretching vibrations. The ESI mass spectrum of phthalimide **5** was dominated by a peak at *m*/*z* 270 $[M\text{–}H^+]^-$. In addition, in the ^{1}H NMR spectrum a broad peak centered at 7.89 ppm was observed for the N–H hydrogen of phthalimide **5** (see Supplementary data, Figs. S11, S14 and S15).

The main hurdle in the synthesis of phthalonitrile **7** was the very strong tendency of the phthalamide **6** to undergo basic hydrolysis to diammonium phthalate and/or ammonium 2-(aminocarbonyl)benzoate. This resulted in a low concentration of the phthalamide **6** in the crude product, which in turn resulted in a low reaction yield of the target phthalonitrile **7**. For example, when the ammonolysis of phthalimide **5** was carried out at 80 °C for 1 h, it was found that the reaction mixture consisted of around 40% of phthalamide **6** and 60% of diammonium phthalate and/or ammonium 2-(aminocarbonyl)benzoate (as judged by the corresponding proton signals intensities in the ^{1}H NMR spectrum, see Supplementary data Fig. S16).

In the final step, phthalamide **6** was converted into the corresponding phthalonitrile **7** by treatment with phosphorus

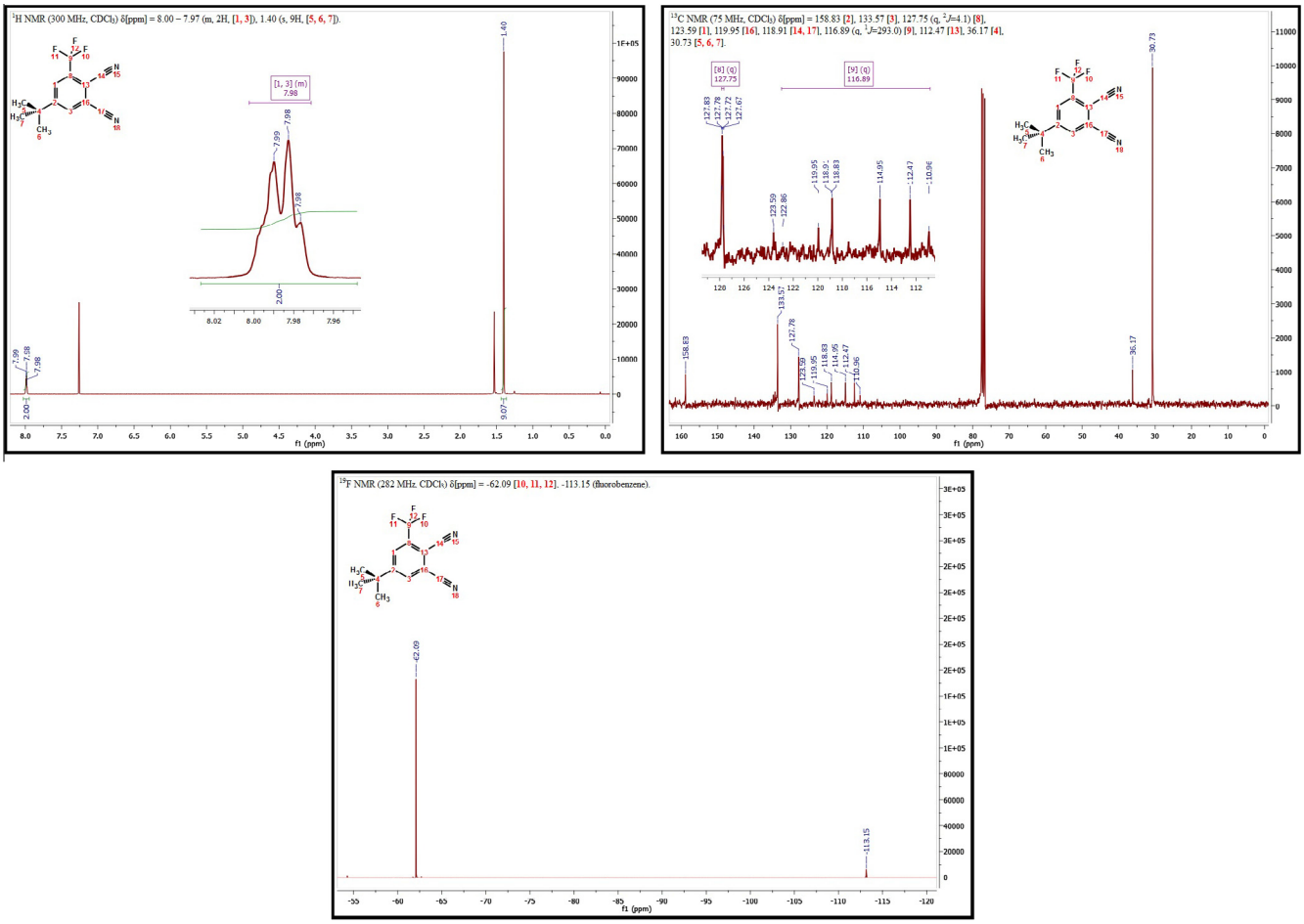


Figure 1. ^{1}H NMR spectrum (upper left), ^{13}C NMR spectrum (upper right), and ^{19}F NMR spectrum (bottom) of 5-*tert*-butyl-3-(trifluoromethyl)phthalonitrile (7).

oxychloride in dry pyridine as a dehydrating agent.[18] After chromatographic separation on silica gel, 5-*tert*-butyl-3-(trifluoromethyl)phthalonitrile (**7**) was obtained in a 23% yield (based on the phthalimide **5**). The ^{1}H NMR spectrum confirmed unambiguously the assigned structure of **7** (Fig. 1). The integration of the signals observed for the *tert*-butyl group and an aromatic ring gave, as expected, a 9:2 ratio. In the ^{19}F NMR spectrum a single peak at −62.09 ppm was attributed to the trifluoromethyl group attached to the aromatic ring (Fig. 1). The IR spectrum of the product showed a sharp peak at 2237 cm^{-1} clearly indicating the presence of the CN groups (aromatic nitriles). The presence of a peak at *m*/*z* 275 [M+Na]$^+$ in the mass spectrum confirmed that the product had been obtained (see Supplementary data, Figs. S21 and S22).

It is worth noting that phthalonitrile **7** could be easily transformed into its more reactive form, namely 6-*tert*-butyl-4-trifluoromethyl-1,3-diiminoisoindoline (**8**). Diiminoisoindolines are very useful precursors for the synthesis of phthalocyanine complexes of less reactive metals, where simple phthalonitriles fail to give the corresponding dye.[7,8] Moreover, 1,3-diiminoisoindolines have found application as precursors for the synthesis of phthalocyanine homologues, viz. subphthalocyanines. Ammonia gas was passed through a methanolic solution of **7** at room temperature with sodium methoxide as the catalyst to afford 1,3-diiminoisoindoline **8** quantitatively. The ESI mass spectrum of **8** was dominated by two peaks: one at *m*/*z* 270 [M+H]$^+$ and the other at *m*/*z* 292 [M+Na]$^+$ (see Supplementary data, Figs. S23 and S24).

In conclusion, we have described a six-step synthesis of a novel CF_3 group containing phthalonitrile. Phthalonitriles are known precursors for the synthesis of phthalocyanines. The phthalonitrile under discussion was converted into its more reactive form, namely 6-*tert*-butyl-4-trifluoromethyl-1,3-diiminoisoindoline **8**.

Acknowledgments

This work operated within the Foundation for Polish Science Team Programme, co-financed by the EU European Regional Development Fund. PolyMed, TEAM/2008-2/6. We would like to thank Professor Jerzy Silberring's team (Department of Biochemistry and Neurobiology, AGH) for performing ESI mass spectra.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.145.

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18. 5-*tert*-Butyl-3-(trifluoromethyl)phthalonitrile (7): Anhydrous pyridine (10 mL) was added to the phthalamide 6 (obtained from 230 mg of phthalimide 5). Next, $POCl_3$ (0.25 mL, 2.68 mmol) was transferred to the flask via a syringe. The mixture was stirred under an inert gas atmosphere for 1 h at 0 C, and then for 1 h at room temperature. The mixture was quenched by pouring onto crushed ice and stirred for 10 min, followed by extraction with CH_2Cl_2 (3×30 mL). The organic phase was washed with 5% HCl solution (2×50 mL) to remove the pyridine and then with water until neutral pH was obtained. After solvent evaporation the residue was subjected to column chromatography (silica gel, acetone/hexane, 2:8). The first colorless fraction was collected and identified as the product. Yield: 50 mg, 23%. ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: 1.40 (s, 9H, *t*-Bu), 7.98 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 158.83, 133.57, 127.75 (q, ^2J = 4.1 Hz), 123.59, 119.95, 118.91, 116.89 (q, ^1J = 293.0 Hz), 112.47, 36.17, 30.73. ^{19}F NMR (282 MHz, $CDCl_3$, fluorobenzene was used as an internal standard) δ [ppm]: −62.09. ESI-MS: m/z = 275 $[M+Na]^+$. FT-IR: ν = 3426 (m), 3089 (m, Ar–H), 2975 (s, C–H), 2959 (s, C–H), 2917 (m, C–H), 2879 (m, C–H), 2237 (s, CN), 1603 (s), 1571 (m), 1480 (s), 1462 (s), 1419 (m), 1402 (m), 1372 (s), 1336 (vs), 1273 (vs), 1249 (s), 1214 (s), 1190 (vs), 1142 (vs), 1094 (s), 909 (s), 873 (m) cm^{-1}. Anal. Calcd for $C_{13}H_{11}N_2F_3$: C, 61.90; H , 4.40; N, 11.10. Found: C, 61.80; H, 4.59; N, 10.73.