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Short Note

2-(2,5-Dimethoxyphenyl)pyrrole-3-carbonitrile

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Abstract: The Cadogan reaction of 2-aryl-3-nitropyridines leads to δ-carbolines. The title compound is a side product in this reaction, generated via a ring opening of a nitrene and cyclization. A crystal structure analysis gives an enormous unit cell.

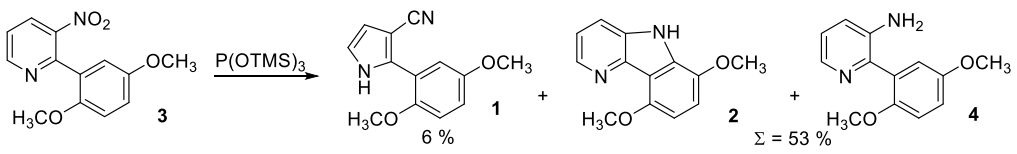
Keywords: Cadogan reaction; electrocyclization; pyrrole; X-ray crystallography; spectroscopy

1. Introduction

Treatment of *o*-nitrobiaryls with phosphorous-III reagents results in a reduction in the nitro group with concomitant ring closure to a pyrrole ring [1–5]. This Cadogan reaction is a successful route for the preparation of carbazoles [6–8], especially applied in the syntheses of alkaloids [9,10]. Higher conjugated systems, e.g., for use in organic electronics, are accessible via multiple Cadogan reactions [11,12]. Furthermore, a plethora of other condensed heterocyclic systems, such as indolopyrroles or carbolines, are also accessible [13–20]. In general, only five-membered rings are closed during the Cadogan reaction, and a very small number of six-membered rings are accessible [18,21]. Mechanistic studies give rise to a nitrene intermediate, but there are also hints of an anionic electrocyclization [2,22]. Cadogan reactions are often accompanied by a large number of byproducts. During our studies on the synthesis of α-carbolines in a Suzuki-Cadogan sequence [20], nitriles appeared as byproducts. The title compound **1** of this report is the byproduct of the synthesis of a dimethoxy-δ-carboline **2**. We present the synthesis, molecular structure and a mechanistic hypothesis for the pyridine-to-pyrrole ring contraction.

2. Results

The starting material for the Cadogan reaction, 2-(2′,5′-dimethoxyphenyl)-3-nitropyridine **3**, was prepared in a microwave-assisted Suzuki–Miyaura coupling of 2-chloro-3-nitropyridine with a 2,5-dimethoxyphenyl boronic acid in 91% yield. The reduction with tris(trimethylsilyl) phosphite was performed under microwave irradiation (Scheme 1). A heterogeneous mixture was obtained, containing mainly the anticipated δ-carboline **2**, accompanied by the aminopyridine **4** as a simple reduction product and the ring-contracted dimethoxyphenylpyrrole carbonitrile **1**. The chromatographic separation provided pyrrole **1** in 6% yield as a colorless solid.



Scheme 1. Phosphite reduction of dimethoxyphenyl-nitropyridine.

The structure of the title compound **1** was analyzed by spectroscopic methods. Although mass spectrometry and the intense nitrile band in the IR gave good hints for the structure, the results for NMR experiments were not beyond any doubt. Therefore, a crystal

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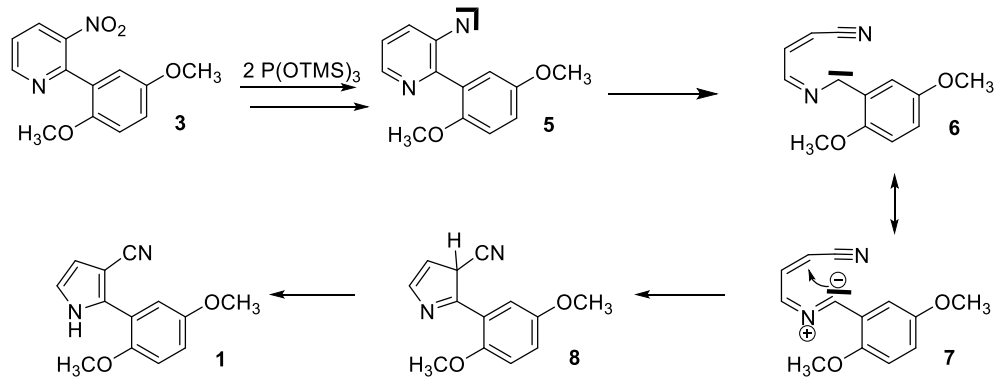
structure analysis (vide infra) was performed and led to the pyrrole carbonitrile structure **1**. For the formation of the ring-contracted product, we assume a stepwise deoxygenation of **3** with phosphite in two subsequent steps until a pyrido-nitrene **5** has been formed. Ring opening leads to carbene **6** with an aryl and a cyanoacrylimine substituent. This carbene is stabilized by two conjugated moieties and can also be described as 1,2-dipole **7**. This process can also be imagined as an electrocyclic process after the attack of the phosphorous atom on the nitroso-oxygen with concomitant loss of phosphate. Cyclization may occur by the attack of the carbene/carbanion at C-3 of the acrylimine segment to form 3-*H*-3-cyanopyrrole **8** and final tautomerization gives the title compound. The process is depicted in Scheme 2.



Scheme 2. Possible pathway for ring contraction.

Crystal Structure

Crystallization of 1 from acetonitrile yielded colorless needles suitable for X-ray diffraction. The monoclinic unit cell has a gigantic volume of 9119.8(7)Å^3 since it contains 32 molecules of **1**. Uniquely, four different but very similar conformers (A, B, C, D) of 1 fill the unit cell, and each of them appears eight times. The molecules are arranged in parallel chains, one with A and B alternating, the next with C and D. The molecules are connected via intermolecular NH-Nitrile bonds (2.12(2) Å). The superposition of A and B in Figure 1 demonstrates a nearly perfect identity.

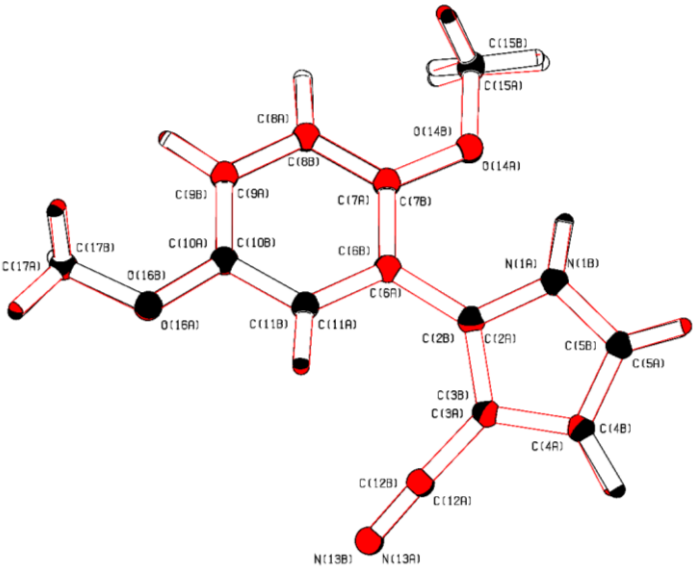


Figure 1. Superimposed conformers A and B of 2-(2,5-dimethoxyphenyl)-1H-pyrrole-3-carbonitrile **1**.

The dihedral angle between the mean planes of the phenyl and pyrrole ring gives the main differences between these conformers. The molecular structure of A may serve as

pars pro toto. The pyrrole ring is completely planar, the *ortho*-carbons of the phenyl ring are not perfectly in the mean plane (deviation $\leq$ 0.011 Å), and both mean planes open a dihedral angle of 24.62(13)°. Surprisingly, both methoxy groups are almost coplanar with the phenyl ring; the small torsion angles are 10.4(4)° for C15-O13-C7-C8 and -6.0(4)° for C17-O16-C10-C9. An intramolecular hydrogen bond connects the pyrrole-N and oxygen of the ortho-methoxy group [23].

3. Discussion

The reduction in the nitro group in a 2-aryl-3-nitropyridine with phosphite gives mainly the desired δ-carboline but also a cyano pyrrole. This stems from a ring contraction of pyridyl nitrene. Although the formation of naphthonitriles in Cadogan reactions has been observed, [20] no reports of the transformation of pyridines to pyrroles have been found. The huge unit cell is filled with eight molecules of four independent conformers each. ^{1}H-NMR spectra of **1**, **2**, **3**; ^{13}C-NMR, HSQC, HMBC, IR and X-ray crystallography data of **3** are in Supplementary Materials.

4. Materials and Methods

4.1. General Information

Solvents and reagents were used as bought if not stated otherwise. NMR-spectra were recorded in deuterated chloroform (dried over potassium carbonate) on a Bruker Avance II HD 300 or Avance III HD 300 (Bruker, Karlsruhe, Germany) with a 5 mm BBFO-head with z-gradient and ATM; interpreted using Mestrenova. The crystal structure was obtained via a STOE IPDS2T (Stoe & Cie, Darmstadt, Germany), and the graphics shown were created with Diamond 3.2 by Crystal Impact. HR-ESI-MS was performed using an Agilent 6545 QTOF-HRAM-MS (Agilent Technologies, Waldbronn, Germany) with ESI source.

4.2. Synthesis

The title compound was obtained during the following two-step procedure: a) 2-(2′,5′-dimethoxyphenyl)-3-nitropyridine: A microwave tube was charged with 2-chloro-3-nitropyridine (164 mg, 1.01 mmol), 2,5-dimethoxyphenylboronic acid (263 mg, 1.44 mmol), 270 mg $NaHCO_3$ 7 mL water, and 7 mL 1,4-dioxane. The mixture was purged with nitrogen for 10 min before tetrakis(triphenylphosphine) palladium(0) (58 mg, 0.05 mmol) was added. The tube was closed and the mixture was heated in the microwave oven at maximum power for 15 min to 125 °C. Thereafter, the cooled mixture was filtered through celite, the residue washed with ethyl acetate and the combined solutions were washed with water and brine, dried over $MgSO_4$, concentrated and the residue purified via chromatography ion silica gel using petroleum ether/ethyl acetate (4/1) (R_f = 0.24)as an eluent. A total of 241 mg (93%) of pure dimethoxyphenyl nitropyridine with m.p. = 91 °C was obtained. ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 8.87 (dd, ^{3}J = 4.7 Hz, ^{4}J = 1.6 Hz, 1 H, 6-H Py), 8.21 (dd, ^{3}J = 8.2 Hz, ^{4}J = 1.6 Hz, 1 H, 4-H Py), 7.43 (dd, ^{3}J = 8.2 Hz, ^{3}J = 4.8 Hz, 1 H, 5-H Py), 7.25 (d, ^{3}J = 3.1 Hz, 1 H, 6-H Ph), 6.98 (dd, ^{3}J = 9.0 Hz, ^{4}J = 3.1 Hz, 1 H, 4-H Ph), 6.84 (d, ^{3}J = 9.0 Hz, 1 H, 3-H Ph), 3.85 (s, 3 H, 2-OCH_3), 3.66 (s, 3 H, 5-OCH_3); IR: $\tilde{v}$ [cm^{-1}] = 1592 m, 1559 m, 1524 s, 1442 m, 1356 s, 1273 w, 1218 m, 1179 w, 1017 m, 856 m, 817 m, 786 m, 745 s, 696 s, 616 m; ESI-MS(+): $[M + H]^+$: calcd.: 261.0870; found: 261.0868.

The reduction in this compound was performed in the following way: 2-(2,5-Dimethoxyphenyl)-3-nitropyridine (71 mg, 0.27 mmol) was dissolved in tris(trimethylsilyl) phosphite (5 mL) in a microwave tube. The stirred mixture was heated to 210 °C for 15 min. The maximum power was 300 W, and the maximum pressure was limited to 10 bar. Thereafter, the mixture was mixed with NaOH (20 mL, 2 M) and stirred for 15 min at ambient temperature. The brown suspension was filtered through celite, the filter cake washed with water (20 mL) and ethyl acetate (80 mL). The aqueous phase was adjusted to pH = 14 and extracted with ethyl acetate (3 × 20 mL). The combined organic solutions were dried ($MgSO_4$), concentrated, and the residue was purified by column chromatography on silica gel using a gradient of petroleum ether/ethyl acetate from 4/1 to 3/7. The first compound

eluted with R_f = 0.2 (PE/EA = 4/1) followed by the anticipated dimethoxybenzopyridoindole and the dimethoxyphenylpyridylamine. The yield of the title compound was 6 mg (6%) of a colorless product. H-NMR: (400 MHz, $CDCl_3$): δ [ppm] = 10.14 (s, 1 H, N-H), 7.81 (d, ^{3}J = 3.0 Hz, 1 H, 6-H Ph), 6.96 (d, ^{3}J = 9.1 Hz, 1 H, 3-H Ph), 6.87 (dd, ^{3}J = 9.0 Hz, ^{4}J = 3.0 Hz, 1 H, 4-H Ph), 6.89 (d, ^{3}J = 8.5 Hz, 1 H, 8-H), 6.81 (t, ^{3}J = 2.8 Hz, 1 H, 5-H), 6.55 (t, ^{3}J = 2.8 Hz, 1 H, 4-H), 4.09 (s, 3 H, 2-OCH_3), 3.85 (s, 3 H, 5-OCH_3); ^{13}C-NMR: (101 MHz, $CDCl_3$): δ [ppm] = 154.37 (C-2 Ph), 149.67 (C-5 Ph), 135.85 (C-2 Py), 118.68 (C-1 Ph), 118.49 (CN), 118.19 (C-5 Py), 115.98 (C-4 Ph), 113.56 (C-4 Py), 113.29 (C-6 Ph), 112.12 (C-3 Ph), 90.15 (C-3 Py), 56.60 (5-OCH_3), 56.02 (2-OCH_3); IR (ATR): $\tilde{\nu}$ = 3378 w, 2925 m, 2854 w, 2214 m, 1734 w, 1612 w, 1557 w, 1505 s, 1466 m, 1439 w, 1379 w, 1268 w, 1225 s, 1186 w, 1102 w, 1044 m, 905 w, 853 w, 803 w, 770 m, 748 m, 687 w cm^{-1}; HR-ESI-MS: [M + H^+]: calcd.: 229.0972, found: 229.0972.

Supplementary Materials: The following supporting information can be downloaded online, ^{1}H-NMR spectra of **1**, **2**, **3**; ^{13}C-NMR, HSQC, HMBC, IR and X-ray crystallography data of **3**.

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