

Communication

The Synthesis and Molecular Structure of 2-(4-Methoxybenzyl)-4-nitro-2*H*-indazole

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Abstract: Two novel indazole derivatives protected with *p*-methoxybenzyl group were synthesized and characterized. The crystal and molecular structure of 2-(4-methoxybenzyl)-4-nitro-2*H*-indazole as one out of the two regioisomers is reported. The compound was obtained from a saturated petroleum ether/ethyl acetate mixture and crystallizes in the triclinic space group $P\bar{1}$. The unit cell parameters are: $a = 6.8994(1)$ Å, $b = 9.8052(2)$ Å, $c = 11.1525(2)$ Å; $\alpha = 71.729(1)^\circ$, $\beta = 79.436(1)^\circ$, $\gamma = 74.349(1)^\circ$ and $V = 685.83(2)$ Å³. There are two independent molecules found in the asymmetric unit.

Keywords: indazoles; protecting group; *p*-methoxy benzyl; X-ray structure

1. Introduction

The indazole structural motif is found in various biological active molecules like compounds with antimicrobial and anti-inflammatory activity [1,2] or Eph receptor inhibitors [3]. Several functionalized 1*H*-indazole cores function as starting material for these pharmacologically relevant substances. To block the nitrogen atoms against nucleophilic attack in further reactions, it is necessary to introduce protecting groups [4]. Furthermore, the blocking of the nitrogen atoms of the indazole moiety is essential for the preparation of highly selective carbon-11 radiotracers based on inhibitors published by Bardelle and co-workers [3]. For this purpose, the *p*-methoxybenzyl moiety (PMB) was chosen as

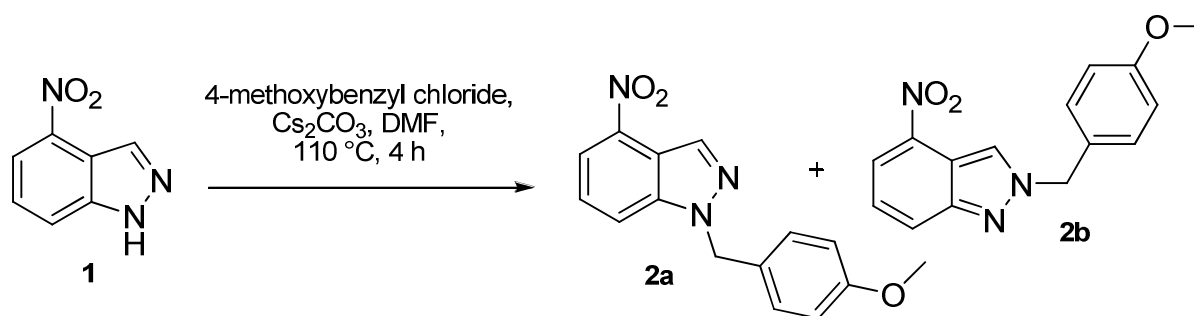
protecting group. The convenient introduction and selective removal of the PMB group is beneficial. The PMB residue can be removed selectively with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) [5] and when adapted to amine protection it can be removed with trifluoroacetic acid at 65 °C [6].

2. Results and Discussion

4-Nitro-1*H*-indazole (**1**) was applied as starting material for the introduction of the PMB protective group and was prepared from 2-nitro-3-methylaniline by diazotation in a high yield [7]. In the next step, **1** was reacted with 4-methoxybenzyl chloride in anhydrous DMF using Cs₂CO₃ as base. The mixture was allowed to stir at 100 °C for two hours. Both regioisomers **2a** and **2b** were obtained as yellow solids after aqueous workup and purification via flash column chromatography in yields of 48% and 28%, respectively (Figure 1).

Single crystals of **2b** with a m.p. 135 °C were obtained during the purification step from a saturated petroleum ether/ethyl acetate solution. Attempts were made to obtain single crystals from **2a** (m.p. 113 °C) as well from various saturated organic solvent solutions, but without success so far. The crystal and instrumental parameters found for compound **2b** and used in the X-ray structure determination are summarized in Table 1. A drawing of the molecular structure of compound **2b** with the atom-labeling scheme (displacement thermal ellipsoids are drawn at the 50% probability level) is shown in Figure 2. Selected bond lengths for the atoms of 2-(4-methoxybenzyl)-4-nitro-2*H*-indazole (**2b**) are given in Table 2.

Figure 1. Synthesis of the *p*-methoxybenzyl protected indazole derivatives **2a** and **2b**.



The structure of **2b** can be described roughly as hook shaped molecules. One almost planar unit consists of the 4-nitroindazole part and the other one comprises the 4-methoxyphenyl moiety. They are connected through the benzylic carbon atom C8. The N2–C8–C9 angle was determined with 111.02(4)°, which is slightly larger than the tetrahedral angle expected for a saturated carbon atom. It is interesting to note that the mean plane through the three atoms of the nitro group is almost in plain with the planar indazole unit (5.5° dihedral angle). Moreover, the carbon atom C15 of the methoxy group attached to the planar phenyl ring of the benzyl moiety is located almost in the plane of this aromatic system. Thus, the molecules of **2b** are constructed by two planar groups of atoms, bent at an angle of 111°. In crystals of **2b**, each hook shaped molecule interlocks with the next one, as shown in Figure 3. All the planes of the atoms of the indazole unit are parallel to each other as well as the planes through the atoms of the benzyl units (see above and also Figure 3). Nevertheless, the indazole planes have a different orientation than the benzyl planes.

Intermolecular contacts are limited to weak, van-der-Waals type interactions. Classical hydrogen bonds are not present, because there are no hydrogen atoms attached to electronegative atoms. The shortest distances between neighboring molecules exist between C-bonded H atoms and the O, N heteroatoms: O1...H7', 2.533 Å; O2...H15', 2.611 Å; O3...H14', 2.573 Å; and N1...H10', 2.745 Å (primed atoms are those of the neighboring molecule).

Figure 2. A view of molecule **2b** showing the atom-labeling scheme. Displacement ellipsoids are drawn at the 50% probability level.

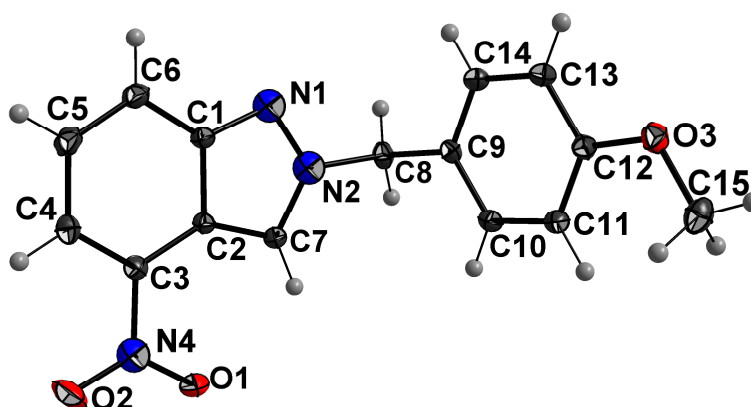
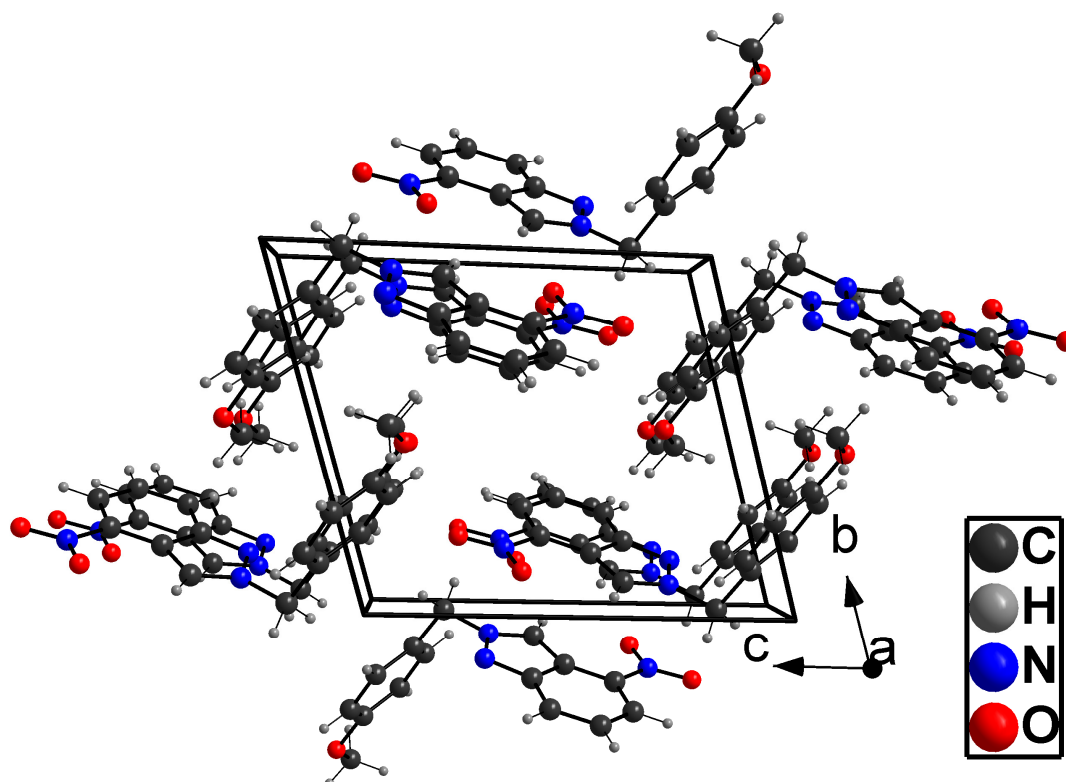


Table 1. Crystal data and structure refinement parameters for compound **2b**.

Crystal data		Refinement	
Formula	C ₁₅ H ₁₃ N ₃ O ₃	Refinement method	Full-matrix least-squares on F^2
Formula weight	283.28 g·mol ⁻¹	Data/restraints/parameters	10467/0/190
Temperature	296 K	Measured reflections	30930
Wavelength	0.71073 Å	Goodness-of-fit on F^2	1.02
Crystal system	triclinic	Final R indices	$R_1 = 0.0428$
Space group	$P \bar{1}$	$[I > 2\sigma(I)]$	$wR_2 = 0.1238$
Unit cell dimensions	$a = 6.8994(1)$ Å $b = 9.8052(2)$ Å $c = 11.1525(2)$ Å $\alpha = 71.729(1)^\circ$ $\beta = 79.436(1)^\circ$ $\gamma = 74.349(1)^\circ$	R indices (all data)	$R_1 = 0.0580$ $wR_2 = 0.1352$
Volume	685.83(2) Å ³	Largest diff. peak/hole	0.66/-0.51 e Å ⁻³
Z	2		
Density (calcd.)	1.372 g·cm ⁻³		
Absorption coefficient	0.10 mm ⁻¹		
$F(000)$	296		
Crystal size	0.36 × 0.34 × 0.28 mm		

Figure 3. View of the crystal packing of **2b** along the crystallographic *a*-axis.**Table 2.** Selected interatomic distances [Å] in **2b**.

atoms	distance	atoms	distance
N1–N2	1.3447(6)	N2–C7	1.3499(6)
C1–N1	1.3536(7)	N2–C8	1.4716(6)
C1–C2	1.4303(6)	C8–C9	1.5083(7)
C2–C3	1.4137(6)	C9–C10	1.3925(7)
C3–C4	1.3768(7)	C9–C14	1.3976(7)
C3–N4	1.4541(7)	C10–C11	1.3949(7)
N4–O2	1.2291(7)	C11–C12	1.3950(7)
N4–O1	1.2321(7)	C12–C13	1.3995(7)
C1–C6	1.4132(7)	C13–C14	1.3884(8)
C2–C7	1.3973(7)	C12–O3	1.3664(6)
C4–C5	1.4178(8)	O3–C15	1.4290(8)
C5–C6	1.3760(8)		

3. Experimental Section

3.1. General

NMR spectra were recorded on a Varian Inova-400 spectrometer at 400 (^1H) and 101 MHz (^{13}C), respectively. The chemical shifts of the spectra are reported in parts per million (ppm) with tetramethylsilane (TMS) as internal standard. The melting points were determined on a Galen III (Cambridge Instruments) melting point apparatus (Leica, Vienna, Austria) and are uncorrected. MS

spectra were obtained on a Micromass Quattro-LC spectrometer using electron spray (ESI) as ionisation method.

3.2. Synthesis of Compounds **2a** and **2b**

4-Nitro-1*H*-indazole (**1**) (820 mg, 5.02 mmol) was dissolved in anhydrous DMF (10 mL), cesium carbonate (1.798 g, 5.52 mmol) and 4-methoxybenzyl chloride (864 mg, 5.52 mmol) were added at ambient temperature. The resulting mixture was allowed to stir 2 h at 100 °C. Afterwards, the reaction was quenched with water and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were separated and dried over Na₂SO₄. The solvent was removed and the residue was purified via flash chromatography (petroleum ether/ethyl acetate 5:1) to yield compound **2a** (677 mg, 48%) and compound **2b** (394 mg, 28%) as yellow solids.

1-(4-Methoxybenzyl)-4-nitro-1*H*-indazole (**2a**). m.p. 113 °C. *R*_f 0.68 (petroleum ether/ethyl acetate 1:1). ¹H NMR (400 MHz, CDCl₃): δ 3.77 (s, 3H, CH₃), 5.62 (s, 2H, CH₂), 6.84 (d, ³*J* = 8.6 Hz, 2H, H-3'/H-5'), 7.17 (d, ³*J* = 8.6 Hz, 2H, H-2'/H-6'), 7.44 (t, ³*J*_{6,5} = 8.4 Hz, ³*J*_{6,7} = 7.7 Hz, 1H, H-6), 7.70 (d, ³*J*_{5,6} = 8.3 Hz, 1H, H-5), 8.13 (d, ³*J*_{7,6} = 7.7 Hz, 1H, H-7), 8.65 (s, 1H, H-3). ¹³C NMR (101 MHz, CDCl₃): δ 53.5 (CH₃), 55.5 (CH₂), 114.5 (C-3'/C-5'), 116.6 (C-7), 117.7 (C-3a), 118.4 (C-5), 125.6 (C-6), 128.0 (C-1', C-7a), 128.8 (C-2'/C-6'), 133.1 (C-3), 141.1 (C-4), 159.7 (C-4'). MS (ESI+): *m/z* (%) 284 (35) [M⁺+H], 121 (100) [PMB⁺].

2-(4-Methoxybenzyl)-4-nitro-2*H*-indazole (**2b**). m.p. 135 °C. *R*_f 0.61 (petroleum ether/ethyl acetate 1:1). ¹H NMR (400 MHz, CDCl₃): δ 3.80 (s, 3H, CH₃), 5.59 (s, 2H, CH₂), 6.91 (d, ³*J* = 8.7 Hz, 2H, H-3'/H-5'), 7.32 (d, ³*J* = 8.7 Hz, 2H, H-2'/H-6'), 7.38 (dd, ³*J*_{6,5} = 8.6 Hz, ³*J*_{6,7} = 7.5 Hz, 1H, H-6), 8.09 (d, ³*J*_{5,6} = 8.6 Hz, 1H, H-5), 8.16 (d, ³*J*_{7,6} = 7.5 Hz, 1H, H-7), 8.51 (s, 1H, H-3). ¹³C NMR (101 MHz, CDCl₃): δ 55.5 (CH₃), 57.9 (CH₂), 114.6 (C-3'/C-5'), 115.3 (C-3a), 120.8 (C-5), 124.3 (C-3), 126.3 (C-6), 126.9 (C-1'), 130.0 (C-2'/C-6'), 140.8 (C-4), 150.1 (C-7a), 160.1 (C-4'). MS (ESI): *m/z* (%) 284 (100) [M⁺+H], 121 (20) [PMB⁺].

3.3. Data Collection and Refinement

Crystallographic data were collected with a Bruker-Nonius Apex-X8 CCD-diffractometer with monochromatic Mo-*K*α radiation (λ = 0.71073 Å) and a CCD detector. Preliminary data of the unit cell dimensions was obtained from the reflex positions of 36 frames, measured in three different directions of the reciprocal space. After completion of the data measurements the reflex intensities were corrected for Lorentz, polarization and absorption effects. The structures were solved by direct methods using SHELXS-97 and refined against *F*² on all data by full-matrix least-squares methods using SHELXL-97 version 2 [8,9]. All non-hydrogen atoms were refined anisotropically; all hydrogen atoms bonded to carbon atoms were placed on geometrically calculated positions and refined using riding models. Crystallographic data has been deposited with the Cambridge Crystallographic Data Centre, CCDC-859297. It can be retrieved free of charge from deposit@ccdc.cam.ac.uk or <http://www.ccdc.cam.ac.uk>.

4. Conclusions

The synthesis and characterization of two novel PMB-protected indazole derivatives has been reported. Furthermore, it was possible to elucidate the molecular structure of the title compound 2-(4-methoxybenzyl)-4-nitro-2*H*-indazole (**2b**) as one out of the two regioisomers. The structure of **2b** can be described roughly as a hook shaped molecule with two almost planar moieties (indazole and methoxyphenyl) connected through a benzylic methylene bridge with an angle of 111°. These data represent a crystallographically characterized example of a *p*-methoxybenzyl protected nitroindazole derivative.

Acknowledgments

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