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Short Note

7-Iodo-1*H*-indole-3-carbonitrile

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Abstract: The title compound was prepared by a Friedel–Crafts acylation-oxime synthesis-decarboxylation/dehydration sequence starting from commercially available 7-iodoindole with 2-(7-iodo-1*H*-indol-3-yl)-2-oxoacetic acid as isolated intermediate. The structural identity of the title compound was proven by elemental analysis and spectroscopic methods (IR, NMR, EI-MS), and purity was assessed by two independent HPLC methods.

Keywords: decarboxylation; dehydration; indole; nitrile; oxime; protein kinase inhibitor

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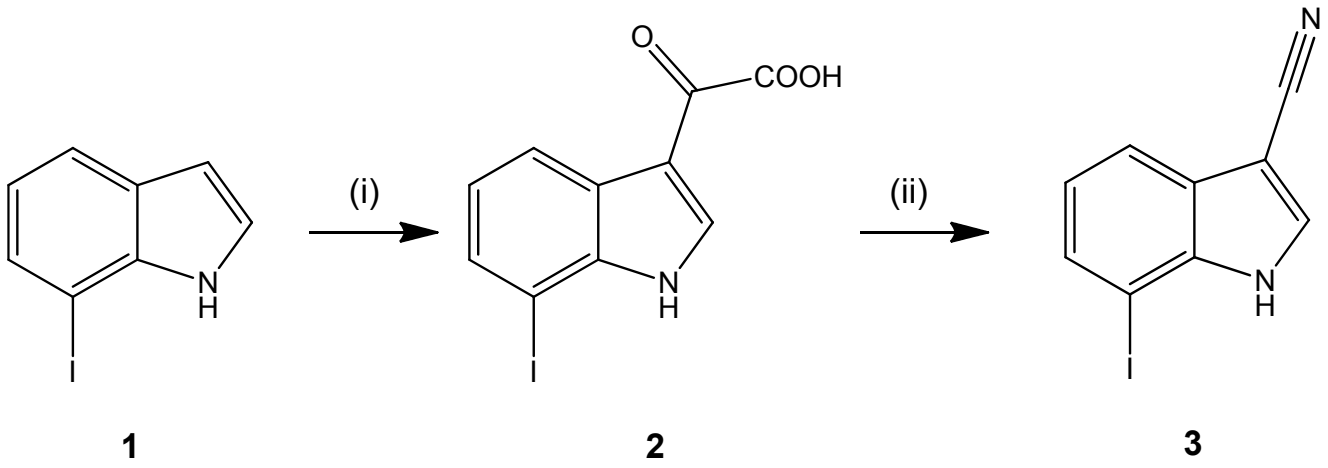
1. Introduction

Protein kinases transfer phosphate groups to the hydroxyl functions of serine, threonine or tyrosine residues of their substrates. Because hyperactivity of protein kinases is involved in many human tumor diseases, more than two dozen small molecular protein kinase inhibitors have been approved by the FDA in recent years as anticancer drugs [1–3]. However, manifold other diseases are also related to protein kinase activity, and therefore current drug development studies in this area are directed towards non-oncologic indications [4], e.g. inflammatory diseases [5,6] and neurodegenerative disorders [7,8]. In our recent research we have focused on the synthesis and discovery of protein kinase inhibitors containing indole partial structures, either as part of annulated ring systems [9–13] or as non-fused structures [14]. With regard to the molecular pharmacology of these inhibitors, the indole core is

frequently an important part of the pharmacophore, displaying interactions with amino acids of the ATP binding pocket of the targeted protein kinase. Recently, it was postulated that protein kinase inhibitors may interact with their targets by halogen bonds [15–18] in addition to other interaction types. Along these lines, we were interested in the title compound **3** as a small core fragment for the development of new protein kinase inhibitors. A literature survey revealed that this compound has not yet been reported. We therefore developed a synthesis procedure starting from commercially available 7-iodoindole (**1**).



Scheme 1. Synthesis of 7-iodo-1*H*-indole-3-carbonitrile (**3**). *Reagents and conditions*: (i) oxalyl dichloride, diethyl ether, ambient temperature, 6 h, 50%; (ii) $H_2NOH \cdot HCl$, NaOAc, EtOH, H_2O, reflux, 7 h, 59%.

2. Results and Discussion

Recently, an elegant method for the Lewis acid catalyzed direct cyanation of indoles in 3-position was published [19]. However, for the preparation of **3** we employed an alternative two-step synthesis sequence which is easy to carry out and also generates a high degree of regioselectivity (Scheme 1). For the first step, commercially available 7-iodoindole (**1**) was reacted with oxalyl dichloride in diethyl ether, furnishing 2-(7-iodo-1*H*-indol-3-yl)-2-oxoacetic acid (**2**) by means of a Friedel–Crafts acylation. Due to the high reactivity of both the aromatic component and the electrophile, addition of a Lewis acid to the reaction mixture was not necessary. To avoid the formation of 1,2-bis(7-iodo-1*H*-indol-3-yl)ethane-1,2-dione as side product, a high excess of oxalyl dichloride was employed in the reaction. The second synthesis step was accomplished by reaction of **2** with hydroxylamine in refluxing ethanol. The initially resulting 2-hydroxyimino derivative was not isolated because the conditions used directly led to the desired nitrile **3** by successive decarboxylation and dehydration. Although a similar decarboxylation/dehydration process of 2-hydroxyimino carboxylic acids was reported more than a century ago [20], it has only rarely been used for the directed preparation of aromatic nitriles. After chromatographic work-up, an analytically pure sample of **3** was prepared by crystallization from ethanol/hexane. Two independent HPLC methods (isocratic and gradient) indicated a degree of purity of the crystalline material sufficient for biological studies

(>95%). The IR spectrum displayed the expected absorption maxima for the N–H (3233 cm^{-1}) and C≡N (2229 cm^{-1}) stretching vibrations.

3. Experimental

3.1. General

7-Iodo-1*H*-indole (**1**) was purchased from Sigma Aldrich (Steinheim, Germany). The solvent diethyl ether was purified and dried by heating at reflux over calcium hydride for 4 h and following distillation. The melting points were detected in open-glass capillaries on an electric variable heater (Electrothermal IA 9100, Bibby Scientific, Stone, UK). The infrared spectra were recorded on a Thermo Nicolet FT-IR 200 spectrometer (Thermo Nicolet, Madison, WI, USA) using KBr pellets. The ^{13}C-NMR and the ^{1}H-NMR spectra were recorded on a Bruker Avance AV III-400 spectrometer (Bruker Corporation, Billerica, MA, USA) (at the NMR Laboratories of the Chemical Institutes of the Technische Universität Braunschweig) in DMSO-d_6. Chemical shifts are presented in relation to TMS (δ = 0 ppm). C nuclei were assigned based on results of ^{13}C-DEPT135 experiments. HPLC was performed on a Merck Hitachi LaChrom Elite system (Hitachi High Technologies Inc., San Jose, CA, USA) (DAD detector: L-2450 (isocratic), UV detector: L-2400 (gradient); pump: L-2130; autosampler: L-2200; column: Merck LiChroCART 125-4, LiChrospher 100 RP-18 (5 µm) (Merck, Darmstadt, Germany); isocratic eluent: acetonitrile/phosphate buffer pH 6 20:80 (compound **2**); acetonitrile/water mixture 50:50 (compound **3**); gradient elution: concentration acetonitrile 0–2 min: 10%; 2–12 min: 10% → 90% (linear) 12–20 min: 90%; elution rate: 1.000 mL/min; detection wavelength: 254 nm and 280 nm (isocratic), 254 nm (gradient); overall run time: 15 min (isocratic), 20 min (gradient); t_s = dead time; t_{ms} = total retention time). Preparation of the phosphate buffer pH 6: 3.5 g K_2HPO_4 were dissolved in water (1 L) and the pH value was adjusted to 6 with phosphoric acid. For mass spectrometry a MAT95XL spectrometer was used (Thermofinnigan MAT, Bremen, Germany, Department of Mass Spectrometry of the Chemical Institutes of the Technische Universität Braunschweig). The elemental analysis was performed on a CE Instruments Flash EA® 1112 Elemental Analyzer (Thermo Quest, San Jose, CA, USA). TLC: Polygram SIL G/UV254, 0.2 mm thickness (Macherey-Nagel, Düren, Germany).

3.2. 7-Iodo-1H-indole-3-carbonitrile (**3**)

To a 100 mL round-bottomed flask containing 7-iodoindole (**1**) (125 mg, 0.514 mmol) in anhydrous diethyl ether (20 mL) was added oxalyl dichloride (1.0 mL, 12 mmol) under exclusion of moisture. The resulting solution was stirred at room temperature for 6 h. After addition of aqueous saturated sodium hydrogen carbonate solution (10 mL) in several small portions stirring was continued at room temperature for 30 min.

After extraction of the organic layer with aqueous saturated sodium hydrogen carbonate solution (2 × 10 mL) the water layer was acidified with concentrated hydrochloric acid (5 mL). After collecting the solid material, it was crystallized successively from *n*-hexane/ethyl acetate (1:1) and petroleum ether/ethanol (20:1) to furnish 81 mg (50%) yellow crystals of 2-(7-iodo-1*H*-indol-3-yl)-2-oxoacetic acid (**2**) [21].

To a 100 mL round-bottomed flask containing hydroxylammonium chloride (79 mg, 1.1 mmol) and sodium acetate (94 mg, 1.1 mmol) in a mixture of ethanol (15 mL) and water (3 mL) was added 2-(7-iodo-1*H*-indol-3-yl)-2-oxoacetic acid (**2**) (181 mg, 0.575 mmol). The mixture was heated at reflux for 7 h. After evaporation of the solvent the crude product was purified by column chromatography (toluene/ethyl acetate 9:1; silica gel) (90 mg, 59%) and crystallized from *n*-hexane/ethanol (10:1) to furnish 58 mg (38%) reddish crystals.

M.p.: 161–163 °C (dec.);

MS (EI. rel. intensity) *m*/*z* (%): 268 ($[M]^{+\bullet}$, 100), 141 ($[M - I]^{+}$, 34);

IR (KBr) (cm^{-1}): 3233 (NH), 2229 (C≡N), 1556, 1518, 1488, 1422, 1241, 1203, 1058, 775, 610;

^{1}H-NMR (400.4 MHz, DMSO-d_6): δ (ppm) = 7.05 (t, 1H, *J* = 7.7 Hz, C(5)H), 7.66 (dd, 1H, *J* = 8.0/1.0 Hz, C(4)H, C(6)H), 7.70 (dd, 1H, *J* = 7.5/0.9 Hz, C(4)H, C(6)H), 8.30 (s, 1H, C(2)H), 12.21 (s, 1H, NH-indole);

^{13}C-NMR (100.7 MHz, DMSO-d_6): δ (ppm) = 118.5, 123.5, 132.5, 135.3 (CH), 78.2 (C(7)), 85.9 (C≡N), 115.9, 127.1, 137.2 (C);

HPLC (AUC%): 99.35% at 254 nm, 99.96% at 280 nm, t_{ms} = 4.07 min, t_s (DMSO) = 1.09 min, (isocratic); 100.00% at 254 nm, t_{ms} = 11.08 min, t_s (DMSO) = 1.26 min (gradient);

TLC (toluene/ethyl acetate 9:1): R_f = 0.36;

Anal. calculated for $C_9H_5IN_2$ (267.95): C, 40.33; H, 1.88; N, 10.45. Found: C, 40.45; H, 1.65; N, 10.11.

^{1}H- and ^{13}C-NMR spectra are reported in the supplementary materials as Figures S1 and S2 together with EI-MS spectrum as Figure S3.

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Author Contributions

Jana Kötz, Sandra I. Schweda: Experimental synthetic work, HPLC, IR and NMR interpretation, writing of manuscript; Rosanna Meine: Experimental synthetic work, literature search, HPLC, NMR and MS interpretation; Hannes Falke: Design of synthesis; Conrad Kunick: Synthesis planning, literature search, writing of manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

Abbreviations

Anal., elemental analysis; EI-MS, electron impact mass spectrometry; HPLC, high performance liquid chromatography; IR, infrared spectrometry; NMR, nuclear magnetic resonance; TMS, tetramethylsilane.

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21. Characterization of **2**: M.p.: 222–223 °C (dec.); MS (EI, rel intensity) *m*/*z* (%): 315 ($[M]^{+\bullet}$, 27), 270 (100), 242 (5); IR (KBr) (cm^{-1}): 3241 (NH/OH), 1745, 1617 (C=O); ^{1}H-NMR (400.4 MHz, DMSO-d_6): δ (ppm) = 7.08 (t, 1H, *J* = 7.8 Hz, C(5)H), 7.7 (dd, 1H, *J* = 7.5/1.0 Hz, C(6)H), 8.20 (dt, 1H, *J* = 7.6/0.6 Hz, C(4)H), 8.37 (d, 1H, *J* = 3.4 Hz, C(2)H), 12.30 (d, 1H, *J* = 3.5 Hz, NH-indole), 14.00 (s, 1H, COOH); ^{13}C-NMR (100.7 MHz, DMSO-d_6): δ (ppm) = 121.1, 124.5, 132.7, 138.1 (CH), 77.96 (C(7)), 113.2, 126.2, 138.6 (C), 164.7 (COOH), 180.8 (C=O); HPLC (AUC%): 99.42% at 254 nm; 99.66% at 280 nm; t_{ms} = 2.97 min, t_s (DMSO) = 1.16 min (isocratic); TLC (toluene/ethyl acetate/formic acid 10:1:1): R_f = 0.26; Anal. calculated for $C_{10}H_6INO_3$ (315.07): C, 38.12; H, 1.92; N, 4.45. Found: C, 37.93; H, 1.80; N, 4.42.