Synthesis of Methyl 5- and 6-Nitroindole-2-carboxylates by Nitration of Indoline-2-carboxylic Acid

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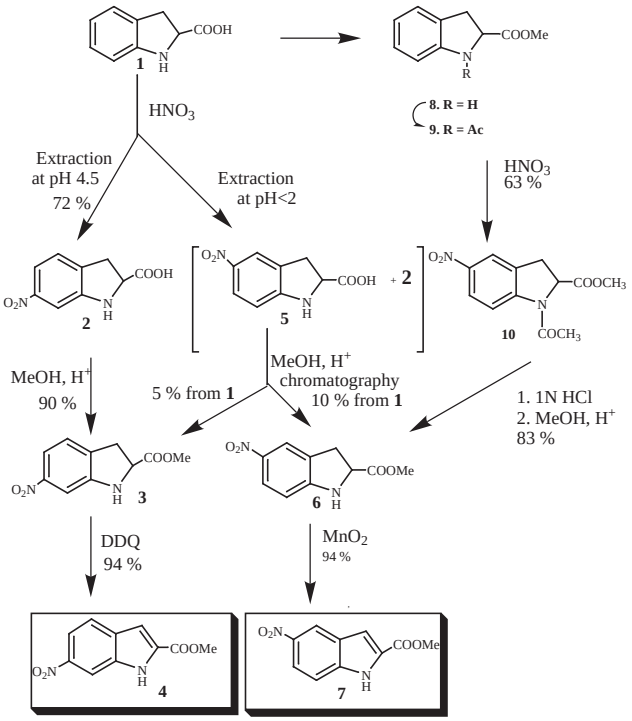
Abstract: Indoline-2-carboxylic acid was transformed into 6-nitroindoline-2-carboxylic acid, the methyl ester of which was easily dehydrogenated by DDQ to methyl 6-nitroindole-2-carboxylate (total yield: 67%). Methyl 5-nitroindole-2-carboxylate was obtained by the nitration of methyl 1-acetylindoline-2-carboxylate acid followed by dehydrogenation with MnO_2 in toluene in 40% total yield.

Key words: methyl 5- and 6-nitroindole-2-carboxylate, indoline-indole method, indoles

Nitroindole-2-carboxylic acids are the precursors of corresponding aminoindole carboxylic acids, which can be used as building blocks in the synthesis of analogs of the antibiotics containing carboxamide moieties (e.g. CC-1065, distamycin, and netropsin) capable of sequence selective DNA interaction. Whereas ethyl 5-nitroindole-2-carboxylate was obtained by Fischer indole synthesis from the 4-nitrophenylhydrazone of ethyl pyruvate in 50–60% yields, ethyl 6-nitroindole-2-carboxylate was obtained from the 3-nitrophenylhydrazone of ethyl pyruvate in 8% yield as a mixture with the 4-nitro isomer.[1–3] Methyl 4,5,6, and 7-nitroindole-2-carboxylates were also obtained by condensation of the corresponding nitrobenzaldehydes with methyl 2-azidoacetate followed by thermolysis.[4] Nitration of protonated indoline leads selectively to 6-nitroindoline, whereas nitration of 1-acetylindoline produces 1-acetyl-5-nitroindoline as protonated nitrogen gives *meta*-direction whereas the non-protonated *N*-acetyl group in indoline shows *para*-direction.[5] We used here this indoline-indole approach for the preparation of nitroderivatives of indole-2-carboxylic acid. Nitration of commercially available indoline-2-carboxylic acid with concentrated HNO_3 in concentrated H_2SO_4 led to a mixture of 6- and 5-nitroindoline-2-carboxylic acids **2** and **5**, in which the 6-nitro derivative **2** was the predominant compound (Scheme). Compound **5** admixed with **2** was extracted with EtOAc at pH < 2, then the aqueous phase was adjusted to pH 4.5–5.0 and extracted with EtOAc, to give 72% of pure 6-nitroindoline-2-carboxylic acid (**2**), which was esterified to give methyl 6-nitroindoline-2-carboxylate (**3**). Additional amounts of **3** (6%) and **6** (10%) were obtained after esterification of the products extracted from the reaction mixture at pH < 2, followed by column chromatography. Dehydrogenation of **3** proceeded under unexpectedly mild conditions (refluxing with DDQ in a EtOAc–benzene mixture) to give the target methyl 6-nitroindole-2-carboxylate (**4**) in 95% yield.



Scheme Synthesis of methyl 6- and 5-nitroindole-2-carboxylates

For the preparation of methyl 5-nitroindole-2-carboxylate (**7**) we used methyl 1-acetylindoline-2-carboxylate (**9**), which was obtained by the acetylation of methyl indoline-2-carboxylate (**8**) (Scheme). Nitration of **9** in concentrated HNO_3–Ac_2O mixture gave methyl 1-acetyl-5-nitroindoline-2-carboxylate (**10**) (63% after column chromatography). Hydrolysis of **10** led to 5-nitroindoline-2-carboxylic acid, which was reesterified without isolation to give ester **6**. All attempts to dehydrogenate compound **6** using DDQ under various conditions were unsuccessful, but refluxing of **6** with fresh γ-MnO_2[6] in toluene gave methyl 5-nitroindole-2-carboxylate (**7**) in 78% yield (40% from **1**). The molecular structures of the compounds obtained were supported by ^{1}H NMR spectroscopy (Table). A significant NOE between NH and 7-H, as well as between 3-H and 4-H for compounds **4** and **7** are strongly indicative for the

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Table ^{1}H NMR Spectra of Compounds **3**,**4**,**6**,**7**,**10**

Compd (Solvent)	Chemical Shifts (δ) and Spin-Coupling Constants *J* (Hz)							
	H-7 [$J_{7,6}$] ($J_{7,5}$)	H-6 [$J_{6,5}$] ($J_{6,4}$) {$J_{6,7}$}	H-5 [$J_{5,4}$] ($J_{5,7}$)	H-4 [$J_{4,5}$] ($J_{4,6}$)	H-3_a [$J_{3a,3b}$] ($J_{3a,2}$)	H-3_b [$J_{3b,3a}$] ($J_{3b,2}$)	H-2 [$J_{2,3a}$] ($J_{2,3b}$)	Other Signals
3 ($CDCl_3$)	7.43 d (2.15)	–	7.60 dd [8.06] (2.01)	7.14 d [8.14]	3.36 m [16.78] (5.35)	3.43 m [17.21] (10.11)	4.43 dd [5.37] (10.12)	CO_2CH_3: 3 H, s 3.76
4 (DMSO-d_6)	8.33 d (2.08)	–	7.91dd [8.89] (2.08)	7.86 d [8.91]	7.29 s	–	–	NH: s, 12.3 CO_2CH_3: 3 H, s 3.95
6 ($CDCl_3$)	7.46 d [8.24]	8.12 dd (2.16) {8.29}	–	8.67 d (2.16)	3.63 dd [17.86] (10.72)	3.29 dd [17.86] (4.58)	5.17 dd [10.76] (4.58)	CO_2CH_3: 3 H, s 3.74
7 (DMSO-d_6)	7.60 d [9.15]	8.17 dd {9.15} (2.34)	–	8.74 d (1.97)	7.43 s	–	–	NH: s, 12.3 CO_2CH_3: 3 H, s, 3.95
10 (acetone-d_6)	8.31d [8.8]	8.16 dd (2.42) {8.8}	–	8.1s	3.77 m	3.48 d [16.53]	5.43 d [10.1]	$COCH_3$: 3 H, s, 2.23 CO_2CH_3: 3 H, s, 3.81

position of the nitro groups: irradiation of 3-H atom (7.39 ppm) in compound **4** led to the enhancement of intensity of the 4-H signal (7.86 ppm, $J_{4,5}$ = 8.91 Hz) by 7%, and irradiation of the 1-H atom increased the 7-H signal (8.33 ppm, d, $J_{7,5}$ = 2.08 Hz) by 20%. Similarly, irradiation of the 3-H atom (7.43 ppm) of **7** increased the intensity of the 4-H signal (8.74 ppm, $J_{4,6}$ = 1.97 Hz) by 8%, and irradiation of the 1-H atom increased the intensity of the 7-H doublet (7.60 ppm, $J_{7,6}$ = 9.15 Hz) by 10%.

In conclusion, we have developed a convenient method for the synthesis of methyl 6-nitroindole-2-carboxylate starting from indoline-2-carboxylic acid. A new method for the synthesis of methyl 5-nitroindole-2-carboxylate was also developed.

Analytical TLC was performed on Kieselgel F_{254} plates (Merck) and column chromatography on silica gel 60 (Merck). Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. 2-Carboxyindoline was purchased from Aldrich.

6-Nitroindoline-2-carboxylic Acid (2)

Indoline-2-carboxylic acid (**1**; 25 g, 153 mmol) was dissolved in 98% H_2SO_4 (200 mL) at –5 °C. Concd HNO_3 (d 1.5 g/cm^3, 6.93 mL, 165 mmol) was slowly added at –20 to –10 °C to the stirred solution. After 30 min of stirring, the reaction mixture was poured into crushed ice (500 g) and extracted with EtOAc. The extract (**a**) was collected for the isolation of 5-nitroindoline-2-carboxylic acid (**5**) (see below). The aqueous phase was adjusted to pH 4.5–5.0 with aq NaOH solution, extracted with EtOAc, and the organic extract was dried (Na_2SO_4). The extract (**b**) was evaporated in vacuo at a temperature below 45 °C (to prevent decarboxylation) to give **2** (23 g, 72%) as a dark yellow oil, which was used for esterification.

Methyl 6-Nitroindoline-2-carboxylate (3) and Methyl 5-Nitroindoline-2-carboxylate (6)

A solution of **2 (**23 g, 111 mmol**)** and *p*-toluenesulfonic acid monohydrate (11 g) in MeOH (100 mL) was refluxed for 30 min, then the solvent was removed in vacuo and the resulting dark solid was dissolved in EtOAc. The solution was washed with sat. aq $NaHCO_3$ solution and then with H_2O until the pH was neutral. The dried solution was evaporated to give methyl 6-nitroindoline-2-carboxylate (**3**; 22 g, 90%) as dark yellow crystals; mp 102–104 °C (MeOH). Additional amounts of **3** and methyl 5-nitroindoline-2-carboxylate (**6**) were obtained from the extract (**a**) after evaporation and stirring in MeOH with *p*-toluenesulfonic acid monohydrate (5 g) for 20 h. After evaporation, the residue was dissolved in EtOAc and washed with aq $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated. The products were isolated by column chromatography (silica gel, *n*-heptane–acetone, 4:1); the fractions with R_f 0.24 (in the same system) gave **6** (2.67 g, 10% from **1**) as yellow powder; mp 124–126 °C (*n*-heptane–acetone) and fractions with R_f 0.32 gave **3** (1.33 g, 5%) (Table).

3

Anal. Calcd for $C_{10}H_{10}N_2O_4$ (222.2): C, 54.05; H, 4.54; N, 12.61. Found: C, 54.06; H, 4.43; N, 12.75.

Methyl 6-Nitroindole-2-carboxylate (4)

A solution of **3** (22 g, 100 mmol) and DDQ (25 g, 110 mmol) in EtOAc–benzene (1:2, 100 mL) was refluxed for 30 min and then diluted with of EtOAc (400 mL). The resulting solution was washed several times with the sat. aq $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated to give **4** (20.7 g, 94%) as yellow powder; R_f 0.80 (*n*-heptane–EtOAc, 2:1); mp 225–227 °C (EtOAc) (Table).

Anal. Calcd for $C_{10}H_8N_2O_4$ (220.2) : C, 54.5; H, 3.66; N, 12.72. Found: C, 54.35; H, 3.68; N, 12.65.

Methyl 1-Acetyl-5-nitroindoline-2-carboxylate (10)

Methyl indoline-2-carboxylate (**8**; 800 mg, 4.5 mmol) was dissolved in Ac_2O (5 mL) and Et_3N (800 μL, 1 equiv) was added. The reaction mixture was stirred at r.t. for 1 h and then poured into a

mixture of ice and aq $NaHCO_3$, and the product was extracted with EtOAc. The extract was washed subsequently with sat. aq citric acid (20 mL), aq $NaHCO_3$, H_2O, brine, then dried and evaporated to give **9** as a brown oil, which was used in the next step without further purification. It was dissolved in Ac_2O (10 mL) and a solution of conc. HNO_3 (300 μL) in Ac_2O (5 mL) was added dropwise at 0 °C. The mixture was stirred for 1.5 h and then poured into a mixture of ice and aq $NaHCO_3$. The product was extracted with EtOAc (100 mL), washed with sat. aq $NaHCO_3$ solution, H_2O and brine, dried, evaporated, and purified by column chromatography (SiO_2, *n*-heptane–EtOAc, 1.5:1) to give **10** as a yellowish solid (750 mg, 63% from **8**); R_f 0.41 (*n*-heptane–EtOAc, 1:1); mp 122–125 °C (*n*-heptane–EtOAc) (Table).

Anal. Calcd for $C_{12}H_{12}N_2O_5$ (264.2): C, 54.55; H, 4.58; N, 10.60. Found: C, 54.38; H, 4.51; N, 10.68.

Methyl 5-Nitroindoline-2-carboxylate (6)

Methyl 1-acetyl-5-nitroindoline-2-carboxylate (**10**; 500 mg, 1.9 mmol) was refluxed in 1 N HCl (25 mL) until dissolution was completed. The reaction mixture was evaporated and dissolved in anhyd MeOH (50 mL), cooled to –10 °C, and treated with $SOCl_2$ (5 mL). It was then left to stir at r.t. overnight. The mixture was evaporated, the residue was dissolved in EtOAc (100 mL), the EtOAc solution was washed with aq $NaHCO_3$, then with H_2O and brine, dried (Na_2SO_4) and evaporated to give crude **6** (350 mg, 83%) (Table).

Methyl 5-Nitroindole-2-carboxylate (7)

Methyl 5-nitroindoline-2-carboxylate (**6**; 50 mg, 0.23 mmol) was dissolved in anhyd toluene (30 mL) and refluxed with freshly prepared γ-MnO_2 (1 g) for 1 h. The reaction mixture was filtered and the filter cake was washed with EtOAc. The washings and the filtrate were colleced and evaporated to give a solid residue, which was washed with Et_2O and dried in vacuo. Recrystallization from toluene gave **7** (40 mg, 78%); mp 290–292 °C (dec.) (Table).

Anal. Calcd for $C_{10}H_8N_2O_4$ (220.2): C, 54.55; H, 3.66; N, 12.72. Found: C, 54.67; H, 3.43; N, 12.75.

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