An Improved Synthesis of Indazole-3-carboxylic Acid

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A new and efficient synthesis of indazole-3-carboxylic acid is reported. The method consists in reacting β-acetylphenylhydrazine with chloral hydrate and hydroxylamine hydrochloride in acidic medium to afford *N*-acetylaminoisonitrosoacetanilide which, in turn, is converted into the title compound by treatment with sulphuric acid.

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Compounds containing indazole moieties have recently attracted much attention as they are being used to investigate the role of indazole as indole bioisostere [1]. From a pharmacological aspect, some indazole derivatives have stimulated interest due to their application as antifertility agents [2] and as antiarthritic agents [3].

Indazole-3-carboxylic acid **1** represents a pivotal intermediate [1] for the preparation of biologically active indazole analogues; other derivatives, however, bearing an oxyalkyl functionalized chain in position 3 of the heterocyclic nucleus have already been synthesized and pharmacologically tested [4].

The reported method for obtaining compound **1** involves reacting 2-(2'-aminophenyl)-glyoxylic acid (readily prepared from isatin) with sodium nitrite, followed by reducing the diazonium salt to the hydrazino group and cyclization [5]. The overall yields are quite low (33%) and rather unreliable, probably due to the diazotation step.

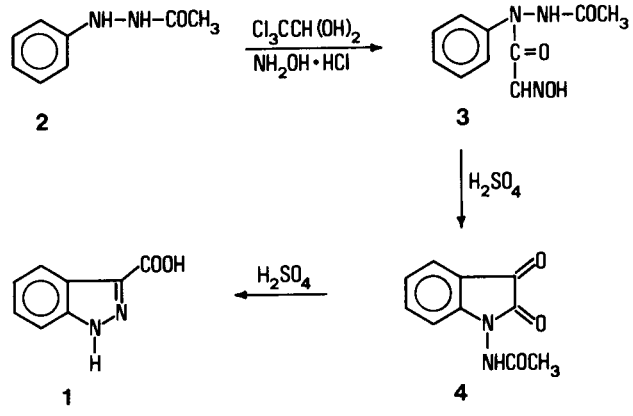
To circumvent the diazotation reaction, an alternative synthetic strategy for indazole-3-carboxylic acid **1** was planned utilizing, as a precursor, *N*-acetylaminoisatin **4**. This compound could have been prepared from β-acetylphenylhydrazine **2** following Sandmeyer's procedure for the synthesis of isatin [6].

As can be seen by the results (Scheme I), the method we describe has the advantages of good yield, low cost starting materials and can be easily scaled up.

By reacting compound **2** with hydroxylamine hydrochloride and chloral hydrate in acidic medium *N*-acetylaminoisonitrosoacetanilide **3** was obtained in 80% yield. The best reaction conditions were the dropping of an aqueous solution of chloral hydrate into a solution of compound **2** in water containing 1*N* hydrochloric acid, sodium sulphate and hydroxylamine hydrochloride at 100°; the reaction was carried out at this temperature for 10 minutes. The use of other acids (*e.g.* acetic acid which leads to a homogeneous reaction mixture at lower temperatures), more prolonged reaction times, higher concentrations of the reactants had deleterious consequences on the yield. Treatment of **3** with concentrated sulphuric acid to promove the Beckmann rearrangement, followed by the hydrolysis of the intermediate *N*-acetylaminoisatin **4** afforded indazole-3-carboxylic acid **1** in 77% yield. Under the experimental conditions described here, compound **4** was always contaminated by the final product **1**. So no attempt was made to isolate and purify compound **4**, this not serving our synthetic purposes. A mass spectrum of the crude product **4** revealed a molecular ion at m/z = 204 followed by the loss of ketene, thus confirming its structure.

A one-pot synthesis from β-acetylphenylhydrazine was also run but with lower overall yield (about 35-40%), indicating that the purity of *N*-acetylaminoisonitrosoacetanilide **3** plays an important role.

Scheme I



EXPERIMENTAL

Infrared spectra were recorded on a Perkin Elmer 457 spectrophotometer. Nuclear Magnetic Resonance spectra were measured in deuteriodimethylsulfoxide with a Varian XL-200 instrument (200 MHz). Mass spectra were obtained with a 7070 EQ spectrometer (direct inlet, 70 eV). Melting points were determined with a Büchi 510 apparatus and are uncorrected. Microanalyses were carried out in the microanalytical laboratory of our department using a Perkin-Elmer 240 instrument.

N-Acetylaminoisonitrosoacetanilide, **3**.

A suspension of β-acetylphenylhydrazine [7] (10.0 g, 0.066 mole), hydroxylamine hydrochloride (15.0 g, 0.216 mole), sodium sulphate (61.6 g, 0.434 mole) in water (200 ml) containing 1*N* aqueous hydrochloric acid (67 ml) was heated to 100°. To the homogeneous solution, a solution of chloral hydrate (13.2 g, 0.079 mole) was rapidly dropped into the reaction mixture and allowed to react at 100° for 10 minutes. After cooling at

room temperature, the solvent was evaporated to half volume. On standing in the refrigerator, a pale yellow solid precipitated. After filtration *in vacuo*, washing with water and drying, *N*-acetylaminoisonitrosoacetanilide **3** (11.6 g, 79%) was obtained, mp 135°; ir (nujol): 3290, 1690, 1669 cm^{-1}; ^{1}H-nmr (deuteriodimethyl sulfoxide): 200 MHz, δ 12.17 (m, 1H), 10.90 (m, 1H), 7.80 (m, 1H), 7.40-7.20 (m, 5H), 1.95 (s, 3H); ms: (70 eV) m/z (relative intensity) 221 (M^+, 10), 179 (40), 176 (95), 150 (75), 107 (100), 91 (90).

Anal. Calcd. for $C_{10}H_{11}N_3O_3$: C, 54.30; H, 4.98; N, 19.00. Found: C, 54.25; H, 4.96; N, 18.95.

Indazole-3-carboxylic Acid **1**.

N-Acetylaminoisonitrosoacetanilide **3** (10.0 g, 0.045 mole) was added portionwise to 96% sulphuric acid (50 ml) at 55°. The reaction mixture was warmed at 85° and reacted at this temperature for 15 minutes. After cooling, the solution was poured into ice (140 g) and the resulting suspension refluxed for 2.5 hours. The precipitate was filtered, washed with water and crystallized from glacial acetic acid. Pure indazole-3-carboxylic acid (5.7 g, 77%) was obtained, mp 267-268°; ir (nujol): 3200, 1680 cm^{-1}; ^{1}H-nmr (deuteriodimethyl sulfoxide): 200 MHz, δ 8.07 (m, 1H), 7.65 (m, 1H), 7.42 (m, 1H), 7.26 (m, 1H); ^{13}C-nmr (deuteriodimethyl sulfoxide): 200 MHz, δ 163.9 (s), 141.1 (s), 136.0 (s), 126.6 (d), 122.7 (d), 122.4 (s), 121.3 (d), 111.1 (d); ms: (70 eV) m/z (relative intensity) 162 (M^+, 100), 145 (28), 118 (27), 91 (8) [8].

Anal. Calcd. for $C_8H_6N_2O_2$: C, 59.26; H, 3.70; N, 17.28. Found: C, 59.20; H, 3.68; N, 17.21.

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[8] This compound has been already reported (see reference [5]), but no spectral data were given.