

A New Synthesis of Indoles

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Keefer and Fodor (1) demonstrated the ability of nitrosamines to form carbanionic species and Seebach and Enders (2) have recently recognized the synthetic potential of this fact. We have experienced this reactivity of nitrosamines with the *N*-nitrosomethylaminobenzophenone **2**. Treatment of **2** with potassium *t*-butoxide in tetrahydrofuran led to the nitrosoindoline **3** in good yield. This

nitrosoindoline offered the possibility for conversion to the 1-aminoindole **6** or to the indole **5**. Hydrogenation of **3** over Raney nickel produced the 3-hydroxyindoline **4** which was found to be surprisingly stable under neutral or alkaline conditions. Catalytic amounts of acid converted it readily to the known 5-chloro-3-phenylindole (3). Reduction of **3** with lithium aluminum hydride led to the 1-amino-3-hydroxyindoline. This compound was not characterized but directly converted to the 1-aminoindole **6** by treatment with ethanolic hydrogen chloride.

The bimolecular analog to this intramolecular reaction also went smoothly. Thus condensation of the *N*-nitrosomethylaniline **7** with benzaldehyde yielded under the same conditions, the nitrosoamine alcohol **8**. Many examples of condensations of nitrosamines with aldehydes have since been reported by Seebach and Enders (2).

In spite of the possible hazard linked to working with nitrosamines, we believe these reactions, including our intramolecular version to have considerable synthetic utility.

EXPERIMENTAL

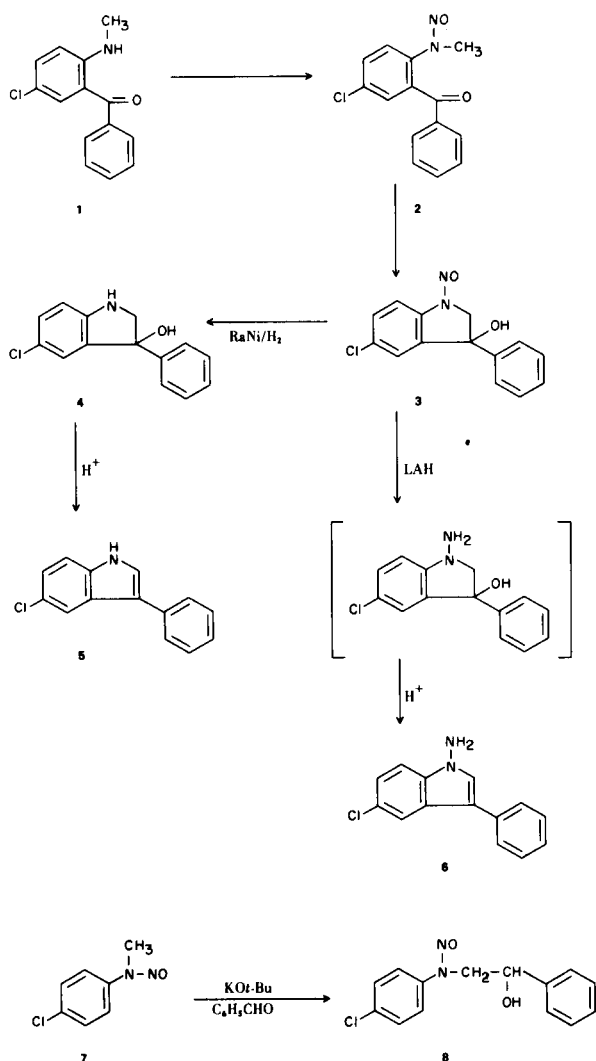
2-Benzoyl-4-chloro-*N*-methyl-*N*-nitrosoaniline (**2**).

A solution of 36 g. (0.52 mole) of sodium nitrite in 100 ml. of water was added at 0-8° to a mixture of 123 g. (0.5 mole) of 2-benzoyl-4-chloro-*N*-methylaniline and 500 ml. of concentrated hydrochloric acid. After addition, stirring was continued for 15 minutes. The precipitated product was collected, washed with water and dissolved in methylene chloride. The solution was dried over sodium sulfate and evaporated. Crystallization of the oily residue from ether/hexane yielded 117 g. (85%) of colorless product with m.p. 111-113°; ν (2-propanol): $\lambda_{\max}$ 249 μ (ϵ 21,700) infl. 285 (7250).

Anal. Calcd. for $\text{C}_{14}\text{H}_{11}\text{ClN}_2\text{O}_2$: C, 61.21; H, 4.03; N, 10.20. Found: C, 61.47; H, 4.01; N, 10.26.

5-Chloro-3-hydroxy-1-nitroso-3-phenylindoline (**3**).

A solution of 27.5 g. (0.1 mole) of 2-benzoyl-4-chloro-*N*-methyl-*N*-nitrosoaniline in 400 ml. of tetrahydrofuran was cooled to -20°. Potassium *t*-butoxide, 12.3 g. (0.11 mole) was added and the mixture was stirred at -10° to 0° for 30 minutes. After addition of 20 ml. of glacial acetic acid the reaction mixture was partitioned between ether and water. The organic phase was separated, dried over sodium sulfate and evaporated. The residue was crystallized from ether/hexane to leave 20 g. (73%) of product with m.p. 149-150°. For analysis it was recrystallized



from methylene chloride/hexane; uv (2-propanol): λ infl. 225 $m\mu$ (ϵ 13,500) max 280 (10,900) 291 (10,200) 309 (10,400); nmr (d-DMSO): δ 4.1 ppm (d, 1) and 4.37 (d, 1) (AB-system, $J = 15$ Hz, $-\text{CH}_2-$) 6.60 (s, 1, OH) 7.06 (d, 1, $J = 2.5$ Hz, $\text{C}_4\text{-H}$) 7.3 (s, 5, C_6H_5) 7.46 (q, 1, $J_{\text{AB}} = 8$ Hz, $J_{\text{AX}} = 2.5$ Hz, $\text{C}_6\text{-H}$) 7.9 (d, 1, $J = 8$ Hz, $\text{C}_7\text{-H}$).

Anal. Calcd. for $\text{C}_{14}\text{H}_{11}\text{ClN}_2\text{O}_2$: C, 61.21; H, 4.03; N, 10.20. Found: C, 61.11; H, 3.97; N, 10.04.

5-Chloro-3-hydroxy-3-phenylindoline (4).

5-Chloro-3-hydroxy-1-nitroso-3-phenylindoline, 2.75 g. (0.01 mole), dissolved in 100 ml. of tetrahydrofuran was hydrogenated over Raney nickel until uptake of hydrogen had stopped (ca. 1 hour). The catalyst was removed by filtration. The filtrate was evaporated under reduced pressure without heat. Crystallization of the residue from ether yielded 1.7 g. (69%) of colorless crystals with m.p. 139-142°. For analysis it was dissolved in cold tetrahydrofuran and crystallized by addition of hexane, m.p. 145-146°; nmr (d-DMSO): δ 3.67 ppm (d, 2, $J = 2$ Hz, $-\text{CH}_2-$) 5.93 (s with broad base, 2, NH and OH) 6.65 (d, 1, $J = 8$ Hz, $\text{C}_7\text{-H}$) 6.82 (d, 1, $J = 2.5$ Hz, $\text{C}_4\text{-H}$) 7.06 (q, 1, $J_{\text{AB}} = 8$ Hz, $J_{\text{AX}} = 2.5$ Hz, $\text{C}_6\text{-H}$) 7.2-8.0 (m, 5, C_6H_5).

Anal. Calcd. for $\text{C}_{14}\text{H}_{12}\text{ClNO}$: C, 68.44; H, 4.92; N, 5.70. Found: C, 68.50; H, 4.92; N, 5.55.

5-Chloro-3-phenylindole (5) (3).

A solution of 1 g. of 5-chloro-3-hydroxy-3-phenylindoline in 20 ml. of methanol containing 2 drops of concentrated hydrochloric acid was heated on the steam bath for 5 minutes. The product was crystallized by partial evaporation and dilution with water to yield 0.85 g. (92%), m.p. 90-92°.

1-Amino-5-chloro-3-phenylindole (6).

A solution of 13.75 g. (0.05 mole) of 5-chloro-3-hydroxy-1-nitroso-3-phenylindoline in 250 ml. of tetrahydrofuran was added to a suspension of 4 g. (0.1 mole) of lithium aluminum hydride in 100 ml. of tetrahydrofuran. During addition the temperature was kept between 10° and 20° and was then allowed to reach 40°. After stirring for 2 hours at room temperature the reagent was hydrolyzed by addition of 20 ml. of water and 250 ml. of ether. The inorganic material was removed by filtration over Celite. The filtrate was dried over sodium sulfate and evaporated.

The residue, which according to the thin layer chromatogram consisted mainly of 1-amino-5-chloro-3-hydroxy-3-phenylindoline, was dissolved in 100 ml. of ethanol and treated with ethanolic hydrogen chloride. The hydrochloride of 1-amino-5-chloro-3-phenylindole was crystallized by partial evaporation and addition of ether to yield 8.5 g. (61%) with m.p. 160-163°.

For conversion to the free base it was partitioned between ether and 10% aqueous sodium carbonate. Crystallization of the evaporated ether layer from methylene chloride/hexane gave yellowish prisms, with m.p. 85-86°; uv (2-propanol): λ max 226 $m\mu$ (ϵ 28,400) sh 235 (27,100) max 268 (16,900) sh 308 (7200); nmr (deuteriochloroform): δ 4.7 ppm (broad s, 2, NH_2) 7-8 (m, 9, aromatic H).

Anal. Calcd. for $\text{C}_{14}\text{H}_{11}\text{ClN}_2$: C, 69.28; H, 4.57; N, 11.54. Found: C, 69.54; H, 4.38; N, 11.48.

4-Chloro-*N*-(2-hydroxy-2-phenylethyl)-*N*-nitrosoaniline (7).

A mixture of 1.7 g. (0.01 mole) of 4-chloro-*N*-methyl-*N*-nitrosoaniline (4), 1.27 g. (0.012 mole) of benzaldehyde, 1.57 g. (0.014 mole) of potassium *t*-butoxide and 40 ml. of tetrahydrofuran was stirred at 5-15° for 1½ hours. After addition of 2 ml. of glacial acetic acid, the reaction mixture was partitioned between water and ether. The organic phase was separated, dried over sodium sulfate and evaporated. Crystallization of the residue from methylene chloride/hexane yielded 1.9 g. (69%) of light tan prisms with m.p. 85-87°. For analysis it was recrystallized from the same solvents; uv (2-propanol): λ infl. 217 $m\mu$ (ϵ 16,500) max 276 (7800) infl. 301 (5200); nmr (d-DMSO): δ ca. 4.1 ppm (m, 2, $-\text{CH}_2-$) (4.75 (broad m, 1, $-\text{CH-O}$) 5.66 (broad d, $J = 4.5$ Hz, OH) 7-7.8 (m, 9, aromatic H).

Anal. Calcd. for $\text{C}_{14}\text{H}_{13}\text{ClN}_2\text{O}_2$: C, 60.77; H, 4.73; N, 10.12. Found: C, 60.78; H, 4.66; N, 10.16.

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