Direct Synthesis of Indole by the Fischer Indole Synthesis

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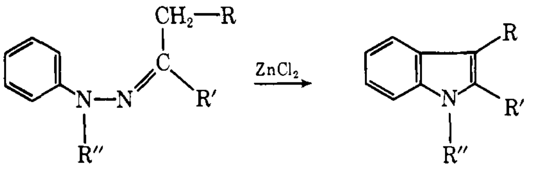
The Fischer indole synthesis has been regarded as the most versatile method for the preparation of indoles. Oddly enough, however, indole (**2a**) itself has not been prepared directly from acetaldehyde phenylhydrazone (**1a**) by the Fischer indole synthesis. Since 1886 when Fischer[1] stated "all trials to obtain indole itself by means of zinc chloride have been so far fruitless", various Lewis acids have been employed only to find complete failure.[2]

Recently, two research groups[3,4] claimed the successful preparation of indole (**2a**) from **1a** using modified alumina catalysts. In this paper we report the first direct synthesis of indole from **1a** by means of zinc chloride (Scheme I), the catalyst originally introduced by Fischer.

Scheme I



1a, R = R′ = R″ = H
b, R = Me; R′ = R″ = H
c, R = R″ = H; R′ = Me
d, R = R′ = H; R″ = Me

2a, R = R′ = R″ = H
b, R = Me; R′ = R″ = H
c, R = R″ = H; R′ = Me
d, R = R′ = H; R″ = Me

Absence of the alkyl group (R) in **1a** should shift the hydrazone–enehydrazine equilibrium[2] away from the enehydrazine form which is necessary for the indolization of **1a**. However, the vulnerability of indole (**2a**) to condensation with the unreacted hydrazone under drastic conditions was thought to be mainly responsible for this notable exception to the Fischer indole synthesis. Thus we assume that Fischer and his successors, using various catalysts, must have had indole in their reaction mixtures, but failed to isolate it because of its fleeting existence. To overcome this difficulty, we used a flow method, with a stream of carrier gas to remove the indole from the contact catalyst immediately after its formation.

Acetaldehyde phenylhydrazone (**1a**) was passed by a stream of nitrogen through a heated combustion tube (290–300 °C) packed with porous glass beads coated with zinc chloride. From the reaction mixture, a 36% yield of indole (**2a**) together with aniline (46%) was isolated. Vapor phase chromatography of the reaction mixture revealed the formation of acetonitrile (10%).

A control experiment without zinc chloride afforded a mixture of aniline and acetonitrile with a trace of indole (**2a**) whose presence was detected by thin layer chromatography.

Application of this method to propionaldehyde and acetone phenylhydrazone (**1b**, **1c**) gave respectively skatole (**2b**) (70%) and 2-methylindole (**2c**) (79%) in good yields, but acetaldehyde 1-methylphenylhydrazone (**1d**) afforded *N*-methylindole (**2d**) in rather low yield (27%).

It is pertinent to note here a rather surprising observation that the vapor phase chromatography of acetaldehyde phenylhydrazone (**1a**) exhibited the peaks corresponding to acetonitrile, aniline, and indole (**2a**); undoubtedly indolization occurs in the metallic injection chamber (250 °C). Formation of the indoles **2b**, **2c**, and **2d** from the corresponding phenylhydrazones **1b**, **1c**, and **1d** was also observed on vapor phase chromatography.

Experimental Section

Melting points and boiling points were uncorrected. Vapor phase chromatography (VPC) was carried out using a JEOL JGC-20K gas chromatograph equipped with a 2-m stainless steel column packed with 5% SE-30 (134 °C) on Chromosorb W for indoles, and a 2-m column with 10% PEG-20M (60 °C) for acetonitrile.

Thin layer chromatography (TLC) employed silica gel G as the support, benzene as the developer, and iodine for detection.

Elemental analyses were performed with a Yanagimoto CHN-Corder Type II. All indoles and their derivatives were identified by comparison with authentic samples.

General Procedure. The apparatus consisted of a reaction tube, 700 mm long and 17 mm in diameter, provided with an inlet tube for the carrier gas and a side arm to which a graduated dropping funnel was connected. The tube was supported in an electrically heated furnace and the lower end of the tube was fitted with a receiver cooled in a dry ice–acetone bath.

The catalyst was prepared by evaporation (in vacuo) of the solvent from a mixture of 2 g of zinc chloride, 20 ml of ethanol, and 34 g of porous glass beads (3 mm diameter). The reaction tube was packed with the catalyst held in place by a glass wool, and was heated to 290–300 °C.

A solution of phenylhydrazone in benzene was introduced from the dropping funnel with a stream of nitrogen (150 ml/min) over 60–80 min. An additional 20 ml of benzene was introduced and the reaction tube was swept with the carrier gas for a further 30 min.

Indole (2a). A solution of 10 g of **1a**, bp 94–96 °C (2 mm), in 20 ml of benzene was introduced in the reaction tube. The product collected in the receiver was analyzed by VPC which showed the presence of indole (**2a**), aniline, and acetonitrile in a ratio of 4:6:1. The reaction product was diluted with ether and extracted with 3% hydrochloric acid. After washing with 3% sodium bicarbonate solution and drying over anhydrous sodium sulfate, the solvent was removed from the ethereal solution to give 3.1 g (36%) of indole (**2a**), which was recrystallized from petroleum ether, mp 52–53 °C (lit.[5] mp 52 °C).

Thy hydrochloric acid extract was made basic with 10% sodium hydroxide solution and extracted with ether. Evaporation of the solvent gave 3.2 g (46%) of aniline, which was identified by conversion into acetanilide, mp 113–114 °C (from ethanol-water).

Starting from a solution of phenylhydrazine (4 g) and paraldehyde (1.6 g) in 10 ml of benzene, **2a** (1.5 g, 36%) and aniline (2.0 g, 56%) were isolated following the same procedure described above.

Skatole (2b). Starting from a solution of 4.6 g of **1b**, bp 105–108 °C (2 mm), in benzene (10 ml), the general procedure furnished skatole (**2b**, 1.8 g, 70%) and aniline (1.1 g, 28%). After recrystallization from ligroin, **2b** melted at 89–91 °C (lit.[6] mp 96 °C).

2-Methylindole (2c). VPC analysis of the reaction product from a solution of 2 g of **1c**, bp 105–108 °C (2 mm), in benzene (4 ml) showed the presence of 2-methylindole (**2c**) and aniline in a ratio of 9:1. From the reaction mixture was isolated 1.4 g of **2c** (79%), mp 58–60 °C (from ethanol-water) (lit.[1] mp 60 °C).

***N*-Methylindole (2d).** The reaction mixture from a solution of 4.6 g of **1d**, bp 105–108 °C (2 mm), in benzene (10 ml) gave 1.1 g (27%) of *N*-methylindole, bp 103–105 °C (2 mm), and 1.4 g (42%) of *N*-methylaniline, bp 121–123 °C (80 mm).

The picrate of **2d** had mp 148–149 °C (from ethanol) (lit.[7] mp 150 °C).

The general procedure starting from a solution of paraldehyde (2 g) and 1-methylphenylhydrazine (5 g) in 15 ml of benzene also afforded *N*-methylindole (**2d**, 1.4 g, 23%) and *N*-methylaniline (19 g, 39%).

Registry No.—**1a**, 935-07-9; **1b**, 7423-16-7; **1c**, 103-02-6; **1d**, 5311-88-6; **2a**, 120-72-9; **2b**, 83-34-1; **2c**, 95-20-5; **2d**, 603-76-9; **2d** picrate, 29052-34-4.

References and Notes

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