NOTES

3,4-Dimethylaniline from Fenchone Using the Schmidt Reaction

BY FREDERIC R. BENSON, LAWRENCE W. HARTZEL AND WALTER L. SAVELL

One of the newer methods for the preparation of 3,4-dimethylaniline which is convenient for laboratory use is that developed by Zaugg.[1] His procedure involves conversion of fenchone to 3,4-dimethylacetophenone, isolation as the oxime, Beckmann rearrangement and subsequent hydrolysis.

In order to reduce the time required for this synthesis, investigation of an alternative method has been made. The modification developed in this laboratory consists of subjecting the crude 3,4-dimethylacetophenone obtained from fenchone to the Schmidt reaction, followed by hydrolysis of the crude 3,4-dimethylacetanilide. The present procedure eliminates the need for isolation of dimethylacetophenone as the oxime and the time consuming Beckman rearrangement. In the method described below the benzene solution of crude dimethylacetophenone, obtained according to Zaugg, is treated directly with hydrazoic acid in benzene to form crude dimethylacetanilide. Hydrolysis and distillation affords a fairly pure product which can be recrystallized to form 3,4-dimethylaniline of good purity. The over-all yield from fenchone of completely purified material is 21%.

A by-product of the Schmidt reaction was obtained in small amounts from one run. This is probably 1-(3′,4′-dimethylphenyl-5-methyltetrazole, although it is possible that it may be the isomer, 1 methyl-5-(3′,4′-dimethylphenyl)-tetrazole.

Experimental

A solution of 126 g. of crude 3,4-dimethylacetophenone in 585 ml. of dry benzene was prepared from 200 g. of commercial fenchone as described by Zaugg.[1]

To a 100-ml. portion of this solution (containing 21.4 g. of 3,4-dimethylacetophenone), mixed with 30 ml. of concentrated sulfuric acid was added with stirring 191 ml. of a 4.1% hydrazoic acid solution in benzene. The temperature was maintained at 38–41° during the addition, which took approximately fifty minutes. After all the solution had been added, the mixture was allowed to stir for five minutes longer, then cooled and poured into a separatory funnel. The sulfuric acid layer was poured into 400 ml. of water and made alkaline with ammonium hydroxide (120 ml.). The yellow oil which separated solidified on cooling. The precipitate was filtered off, washed once with water and refluxed for two hours with 75 ml. of concentrated hydrochloric acid. The solution was poured into 250 ml. of water, extracted with ether, and made alkaline with 6 *N* sodium hydroxide. The alkaline solution was extracted with ether, the ether solution dried over potassium hydroxide and distilled to yield 7.0 g. of crude 3,4-dimethylaniline, b. p. 138–143° (55 mm.), m. p. 47°. On recrystallization from light petroleum ether 5.7 g. of pure 3,4-dimethylaniline was obtained (21% yield from fenchone), m. p. 50–51°. Purity by titration with perchloric acid in glacial acetic acid, 99.1%.

In another experiment conducted as described above, except that the temperature of the Schmidt reaction was maintained at 10–15°, the ether extract of the acid hydrolysis product was allowed to evaporate. The dark, gummy crystals obtained were dissolved in boiling water and treated with charcoal. On filtration and cooling, white crystals separated. A second recrystallization from water afforded 100 mg. of white glistening crystals melting at 111–111.5°.

Anal. Calcd. for $C_{10}H_{12}N_4$: C, 63.80; H, 6.43; N, 29.77. Found: C, 63.95; H, 6.25; N (Dumas), 29.95.

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(1) Zaugg, THIS JOURNAL, **67**, 1861 (1945).

Synthesis of 1-Aminofluorene

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In view of the widespread current interest in the unusual carcinogenic properties of 2-aminofluorene,[2] we wish to report at this time the preparation of the isomeric 1-aminofluorene. The synthesis consisted essentially of the oxidation of fluoranthene to fluorenone-1-carboxylic acid, reduction of the latter to fluorene-1-carboxylic acid and replacement of the carboxyl group by an amino group.

Experimental[3]

Fluorenone-1-carboxylic Acid. I.—Fluoranthene was purchased from the Reilly Tar and Chemical Company. It had a melting point of 107.0–109.4°. Careful chromatography on alumina–celite and determination of the ultraviolet absorption spectra of the fractions showed the presence of a small quantity of pyrene and the probable presence of phenanthrene as impurities. Sulfuric acid extraction of a tetrachloroethane solution of the fluoranthene,[4] resulted in a spectrographically pure fluoranthene, m. p. 110.4–111.2°. On a large scale, the purification was more conveniently achieved by heating fluoranthene at 200° with sodium for half an hour. The fluoranthene was distilled, b. p. 180–90° (4–5 mm.) and the distillate crystallized from ethanol whereby colorless material, m. p. 110.4–111.4°, was obtained. This fluoranthene (95 g.) was oxidized with chromic acid in acetic acid according to the directions of Fieser and Seligman.[5] The procedure for the isolation of the product was simplified as follows:

(1) We wish to thank the John Simon Guggenheim Foundation for a fellowship grant to M. O. which made this work possible. Present address, U. S. Bureau of Mines, Pittsburgh, Pa.

(2) Wilson, De Eds and Cox, *Cancer Research*, **1**, 595 (1941); Bielschowsky, *Brit. med. Bull.*, **4**, 382 (1947); Pinck, *Ann. New York Acad. Sci.*, **50**, 1 (1948).

(3) All melting points corrected.

(4) Compare the purification of chrysene: Fieser, "Chemistry of Natural Products Related to Phenanthrene," 2nd edition, Reinhold Publishing Corp., New York, N. Y., 1937, p. 19.

(5) Fieser and Seligman, THIS JOURNAL, **57**, 2174 (1935).

After the acid was precipitated by dilution with ice and water, the product was filtered and washed twice with hot water. The product was digested in warm, dilute hydrochloric acid, filtered and washed well with hot water. The insoluble material was digested in 500 cc. of water containing 45 g. of sodium carbonate. The hot solution was treated with norite and filtered. The filtrate was acidified with cold, concentrated hydrochloric acid and the precipitate filtered and dried overnight at 80°. Crystallization from acetic acid gave 55.5 g. of the desired acid, brownish-red needles, m. p. 193.4–195.4°. A sample recrystallized from acetic acid had a melting point of 196.8–197.6°. The alkali insoluble material was treated with aqueous sodium bisulfite,[6] the mixture filtered and the filtrate acidified with concentrated sulfuric acid. The precipitated material was filtered and twice recrystallized from ethanol giving red brown crystals of fluoranthenequinone, m. p. 193.0–193.8°.[7]

Ethyl Fluorenone-1-carboxylate.—The keto acid, I, was esterified with ethanol and hydrogen chloride in the usual way. The ester was isolated as gold-yellow crystals after two crystallizations from ethanol, m. p. 84.8–85.4°; reported melting point, 75–76°[8] and 84–86°.[9] On a third recrystallization from ethanol, the crystals had a melting point of 76.0–76.5°. After melting, the melt was cooled and the solid remelted whereupon softening took place at 76° and sharp liquefaction occurred at 84.0–84.8°. Both the high and low melting forms gave identical ultraviolet absorption spectra.

Methyl Fluorenone-1-carboxylate.—This compound was prepared from I with methanol and hydrogen chloride and was crystallized from methanol as yellow needles, m. p. 86.6–87.4°; reported[9] melting point, 86–89°.

Fluorenone-1-carboxamide.—The keto acid, I, was converted *via* the chloride to the amide which was crystallized from acetic acid and separated as yellow-orange crystals, m. p. 235.8–237.0°; reported melting point, 229–230°,[8] and 226.5–227°.[10]

1-Aminofluorenone.—The Hofmann reaction on the amide gave the aminofluorenone. The amine was recrystallized first from ethanol and then from petroleum ether and was thus obtained as orange plates, m. p. 119.0–120.0°; reported melting point, 110°[8] and 118–118.5°.[10]

Fluorene-1-carboxylic Acid, II.—The keto acid, I, was reduced by the Huang-Minlon modification[11] of the Wolff–Kishner reduction. A mixture of 16.6 g. of I, 10 g. of sodium hydroxide, 10 cc. of 85% hydrazine hydrate and 130 cc. of trimethylene glycol was refluxed for three hours. The temperature of the boiling contents was about 150°. The condenser was removed and the boiling continued in the open (hood) until the temperature in the flask was about 205°. At this point refluxing was resumed and continued for two and one-half hours. The mixture was cooled and poured into ice and hydrochloric acid. The precipitate was filtered and dried overnight. Crystallization from acetic acid gave 13.0 g., m. p. 246–249° as a first crop and 1.0 g., m. p. 243–246° (90% yield) as a second crop. The reduction of the keto acid has been done previously[5] with sodium amalgam but in much poorer yield and we are indebted to Dr. Fieser for suggesting the application of the above procedure to improve his yield.

Methyl Fluorene-1-carboxylate, III.—A suspension of 5.16 g. of II in 100 cc. absolute methanol was saturated with hydrogen chloride and the ester isolated in the usual way. Crystallization of the ester from methanol gave 4.94 g. of colorless crystals, m. p. 86.6–87.4°. *Anal.* Calcd. for $C_{15}H_{12}O_2$: C, 80.3; H, 5.4. Found: C, 80.4; H, 5.2.

Ethyl fluorene-1-carboxylate was prepared from ethanol and II as above. Crystallization from ethanol gave colorless crystals, m. p. 53.6–54.8°. *Anal.* Calcd. for $C_{16}H_{14}O_2$: C, 80.7; H, 5.9. Found: C, 80.9; H, 5.8.

Fluorene-1-carboxamide was prepared from II *via* the acid chloride. Crystallization from acetic acid gave colorless crystals, m. p. 251.0–253.0°. *Anal.* Calcd. for $C_{14}H_{11}ON$: C, 80.4; H, 5.3. Found: C, 79.8; H, 5.1.

Hydrazide of Fluorene-1-carboxylic Acid, IV.—A solution of 5.0 g. of the methyl ester, III, 20 cc. of absolute ethanol and 5 cc. of 85% hydrazine hydrate was refluxed for twenty-four hours. A white solid appeared during the refluxing. The mixture was cooled and filtered and washed with ethanol to give 3.84 g. of white fluffy needles, m. p. 216.6–218°. *Anal.* Calcd. for $C_{14}H_{12}N_2O$: N, 13.2. Found: N, 13.0.

1-Fluorenylurethan, V.—A solution of 1.06 g. of IV in 20 cc. of glacial acetic acid was treated with 0.5 cc. of concentrated hydrochloric acid. The suspension was cooled to 0° and 0.8 g. of sodium nitrite in 5 cc. of water added. The suspension was stirred in the cold for one hour then at room temperature for one hour. The mixture was diluted with water and filtered. The precipitate was washed with water and dried in a vacuum desiccator. The solid weighed 1.00 g.; it melted at 85° with gas evolution and was very soluble in organic solvents. *Anal.* Calcd. for $C_{14}H_9N_3O$; N, 17.9. Found: N, 18.6. A solution of 0.85 of the crude azide in 25 cc. of absolute ethanol was warmed to about 70°. Rapid gas evolution occurred. The solution was then refluxed for two hours. The solution was filtered from a small amount of insoluble material and the filtrate concentrated. The urethan (0.62 g.) was obtained from ethanol as colorless plates, m. p. 132.0–132.6°. *Anal.* Calcd. for $C_{16}H_{15}NO_2$: N, 5.6. Found: N, 5.8.

1-Aminofluorene.—A mixture of 0.5 g. of the urethan, V, 10 cc. of acetic acid and 15 cc. of concentrated hydrochloric acid was heated in a sealed tube at 140° for four hours. After cooling, the tube was opened, the contents diluted with water and filtered. The insoluble material (m. p. > 270°) was placed in a separatory funnel with 10% potassium hydroxide solution and ether. After shaking for several minutes, the solid disappeared. The ether layer was separated and evaporated to dryness and the residue crystallized from dilute ethanol to give 0.31 g. of tan crystals, m. p. 117–119°; recrystallized from benzene–petroleum ether, m. p. 124.0–124.6°. *Anal.* Calcd. for $C_{13}H_{11}N$: N, 7.7. Found: N, 8.0. The trinitrofluorenone complex[12] separated from benzene as beautiful, almost black needles, m. p. 211.0–211.8°. *Anal.* Calcd. for $C_{26}H_{16}N_4O_7$: N, 11.3. Found: N, 11.3.

(6) The procedure described in *Org. Syntheses*, **24**, 1 (1944), for the isolation of acenaphthenequinone was used.

(7) Fittig and Liepmann, *Ann.*, **200**, 5 (1879).

(8) Goldschmeidt, *Monatsh.*, **23**, 894 (1902).

(9) Goldschmeidt and Lipschitz, *ibid.*, **25**, 1175 (1904). In this article the authors state that the melting point of 75–76° reported for the ethyl ester in their earlier work (ref. 8) was a misprint. However, in view of our isolation of a low melting form, it is quite possible that their early observation was genuine. The melting point of our low melting form did not change even after standing more than a year.

(10) Huntress, Pfister and Pfister, THIS JOURNAL, **64**, 2846 (1942).

(11) Huang-Minlon, *ibid.*, **68**, 2487 (1946).

(12) Orchin and Woolfolk, *ibid.*, **68**, 1727 (1946); Orchin, Reggel and Woolfolk, *ibid.*, **69**, 1225 (1947).

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On the Structure of Aromatic Aldehyde Semicarbazones[1]

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By chemical evidence, structure (I) has been attributed to the semicarbazones. The enolic structure (II), although it might explain the abnormal ultraviolet absorption maximum of these compounds, has been ruled out, since essentially

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