Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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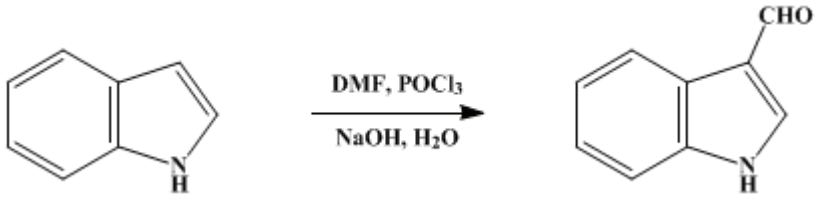
INDOLE-3-ALDEHYDE

[Indole-3-carboxaldehyde]



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1. Procedure

In a 1-l. round-bottomed, three-necked flask fitted with an efficient mechanical stirrer, a drying tube containing Drierite, and a 125-ml. dropping funnel is placed 288 ml. (274 g., 3.74 moles) of freshly distilled dimethylformamide (Note 1). The flask and its contents are cooled in an ice-salt bath for about 0.5 hour, and 86 ml. (144 g., 0.94 mole) of freshly distilled phosphorus oxychloride (Note 2) is subsequently added with stirring to the dimethylformamide over a period of 0.5 hour. The pinkish color of the formylation complex may be observed during this step. The 125-ml. dropping funnel is replaced with a 200-ml. dropping funnel, and a solution of 100 g. (0.85 mole) of indole (Note 3) in 100 ml. (95 g., 1.3 moles) of dimethylformamide is added to the yellow solution over a period of 1 hour during which time the temperature should not rise above 10°. Once the solution is well mixed, the dropping funnel is replaced with a thermometer, and the temperature of the viscous solution is brought to 35°. The syrup is stirred efficiently at this temperature for 1 hour, or for 15 minutes longer than is necessary for the clear yellow solution to become an opaque, canary-yellow paste (Note 4). At the end of the reaction period, 300 g. of crushed ice is added to the paste (Note 5) with careful stirring, producing a clear, cherry-red aqueous solution.

This solution is transferred with 100 ml. of water to a 3-l. three-necked flask containing 200 g. of crushed ice and fitted with an efficient mechanical stirrer and a separatory funnel containing a solution of 375 g. (9.4 moles) of sodium hydroxide in 1 l. of water. The aqueous base is added dropwise with stirring until about one-third of it has been added (Note 6). The remaining two-thirds is added rapidly with efficient stirring (Note 7), and the resulting suspension is heated rapidly to the boiling point and allowed to cool to room temperature, after which it is placed in a refrigerator overnight. The precipitate is collected on a filter and resuspended in 1 l. of water. Most of the inorganic material dissolves, and the product is then collected on a filter, washed with three 300-ml. portions of water and air-dried, yielding about 120 g. (97%) of indole-3-aldehyde, m.p. 196–197°. The indole-3-aldehyde resulting from this procedure is sufficiently pure for most purposes, but it may be recrystallized from ethanol if desired (Note 8).

2. Notes

1. Freshly distilled Merck reagent grade or du Pont technical grade, dimethylformamide, b.p. 151–153°, was used.
2. Mallinckrodt analytical reagent grade phosphorus oxychloride was freshly distilled, b.p. 106–108°.
3. Dow Chemical Company indole was employed. It was recrystallized once (150 g. per 1.8 l.) from 60–90° petroleum ether, m.p. 52–53°.
4. The precipitation described here did not occur in all runs, but no appreciable effect on the yield or purity of the final product was noticed if the stirring and heating of the greenish yellow solution were continued for at least one hour.
5. Reaction between the non-aqueous paste and water (or ice) is exothermic, so it is sometimes helpful to cool the paste in an ice bath before adding the ice. In any case, no trouble should be encountered

provided the 300 g. of ice is added at once.
6. The point at which rapid addition should begin is easily recognized by the disappearance of the red color of the solution and the appearance of a greenish blue or greenish yellow color.
7. Near the end of the addition, the entire contents of the flask may set up solid, stopping the stirrer. The use of a powerful stirrer at this point is desirable, for by the addition of about 100 ml. of water with rapid stirring, the cake is returned to the condition of a thick slurry. During the heating period which follows, the setting-up may again occur, but rapid and efficient stirring is usually sufficient to break up the cake. By the time the temperature has reached the boiling point, a clear yellow-orange solution should be obtained.
There is considerable evolution of dimethylamine during the heating period, especially near the boiling point.
8. About 8.5 ml. of 95% ethanol is required per gram of aldehyde. The recovery of aldehyde in this recrystallization is seldom better than 85%, and the melting point is raised only 1–2°. Concentration of mother liquors to about 15% of their original volume yields another 12–13% of aldehyde which is nearly as pure as the first crop.

3. Discussion

Indole-3-aldehyde may be prepared by direct formylation of indole with dimethylformamide[2,3] or N-methylformanilide[4] using phosphorus oxychloride as a catalyst, by the Reimer-Tiemann reaction,[5,6] by a modified Gattermann reaction on 2-carbethoxyindole,[6] by formylation of the potassium salt of indole with carbon monoxide under vigorous conditions of heat and pressure,[3] by the Grignard reaction,[7] by hydrolysis and decarboxylation of the anil of 3-indolylglyoxylic acid,[8] by a modified Sommelet reaction on gramine[9] and on indole itself,[10] and by oxidation and hydrolysis of N-skatyl-N-phenylhydroxylamine.[11] The method described above is essentially that of Smith.[2] It is far superior to other methods reported for the preparation of indole-3-aldehyde because it is extremely simple and convenient, the yield of aldehyde is nearly quantitative, and the product is obtained in a state of high purity. Two other examples of the use of the dimethylformamide procedure are described in *Organic Syntheses* (pp. 331, 831).

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 656

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

petroleum ether

anil of 3-indolylglyoxylic acid

N-skatyl-N-phenylhydroxylamine

ethanol (64-17-5)

sodium hydroxide (1310-73-2)

carbon monoxide (630-08-0)

Phosphorus Oxychloride (21295-50-1)

dimethylamine (124-40-3)

N-methylformanilide (93-61-8)

dimethylformamide (68-12-2)

Indole (120-72-9)

Indole-3-aldehyde,
Indole-3-carboxaldehyde (487-89-8)

2-carbethoxyindole (3770-50-1)

gramine (87-52-5)

potassium salt of indole