



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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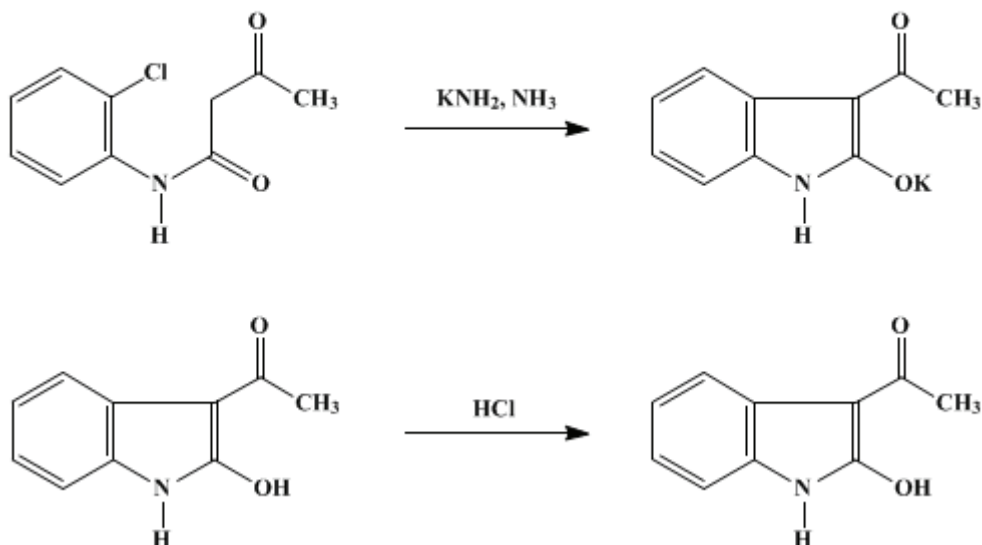
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 5, p.12 (1973); Vol. 40, p.1 (1960).

3-ACETYLOXINDOLE

[Oxindole, 3-acetyl-]



Submitted by J. F. Bunnett, B. F. Hrutfiord, and S. M. Williamson¹.

Checked by B. C. McKusick and D. C. Blomstrom.

1. Procedure

An apparatus resembling that pictured by Schlatter² is assembled in a good hood. Two 5-l. three-necked flasks are mounted side by side about 10 cm. apart and about 10 cm. above the bench top or stand base. These are referred to as the "left" and "right" flasks. Each flask is provided with a dry ice condenser in the outermost neck, and each condenser is protected from the air by a soda-lime drying tube. Each flask is provided through the center neck with a motor-driven stirrer. The left stirrer should have a large sweep blade, and the right stirrer should have a small propeller-type blade. The bearing on each stirrer should be capable of holding a small positive pressure (the submitters used ball-joint bearings). The innermost neck of each flask is fitted with a two-holed rubber stopper. One hole in each stopper is for **nitrogen** supply; a short piece of glass tubing is inserted through each stopper, and these pieces of glass tubing are connected by rubber tubes to a glass "Y" tube which in turn is connected by rubber tubing to a tank of dry **nitrogen**. The rubber tubes between the "Y" tube and the flasks are provided with pinch clamps so that the flow of **nitrogen** can be directed into either flask or into both at once. The other hole in each stopper is for transfer of liquid **ammonia** from the right flask to the left. A glass tube reaching to the very bottom of the right flask is inserted through the right stopper. A glass tube is inserted through the left stopper so that it projects only a few centimeters into the left flask. These glass tubes are bent so that they point toward each other, and they are connected by a piece of rubber tubing provided with a pinch clamp.

With **nitrogen** flowing and all pinch clamps open, the apparatus is flamed to drive away traces of moisture. The condensers are then provided with dry ice covered by **isopropyl alcohol**, and the lower part of the right flask is embedded in crushed dry ice. Liquid **ammonia** (4 l.) is introduced into the right flask through the **nitrogen** inlet from which the rubber tubing is temporarily disconnected, and 105.8 g. (0.5 mole) of *o*-acetoacetochloroanilide (**Note 1**) is placed in the left flask. In order to destroy any water in the **ammonia**, the right stirrer is started and small pieces of **potassium** metal are dropped into the **ammonia**, by briefly lifting the right two-holed stopper, until the blue color persists for 3 minutes. The

nitrogen connection to the left flask is clamped shut and, by partially blocking the escape of **nitrogen** from the right drying tube, about 1 l. of **ammonia** is forced into the left flask. The connection between the two flasks is now clamped shut. Brief operation of the left stirrer facilitates solution of the *o*-acetoacetochloroanilide in the **ammonia**.

Potassium metal (78 g.; 2 moles) is cut into chunks just small enough to pass through the neck of the right flask; these are stored in a beaker under **xylene** until needed. About 5 g. of **potassium** is introduced into the right flask by briefly lifting the two-holed stopper. The right stirrer is started and the **potassium** is allowed to dissolve. To the resulting deep blue solution is added 0.1 g. of finely crushed **ferric nitrate hydrate**, a catalyst for the reaction of **potassium** with **ammonia**. The solution should begin to boil with evolution of **hydrogen**. (*Caution: No flames or sparks should be nearby.*) The rest of the **potassium** is added at such a rate as to maintain active gas evolution (Note 2). Stirring is continued in the right flask until all the **potassium** is consumed, i.e., until the blue color disappears. The right flask now contains a solution of **potassium amide** in liquid **ammonia**; 30–60 minutes is required for its preparation.

The tube between the two flasks is opened by releasing the pinch clamp, and the left stirrer is started. With **nitrogen** flow to the left flask still blocked, the **potassium amide** solution is caused to flow into the left flask by partially blocking the right **nitrogen** exit. The solution in the left flask slowly assumes a chartreuse color. As soon as the right flask is as nearly empty as the apparatus will permit, **nitrogen** flow is opened to the left flask and closed to the right flask and the connection between the two flasks is clamped shut. The right flask is then disconnected and immediately cleaned by rinsing it carefully with ethyl or isopropyl alcohol to destroy **potassium amide** and then washing it with water. (*Caution: Potassium amide is inflammable and will ignite on contact with moisture.*)

The solution in the left flask is stirred for 30 minutes after all the **potassium amide** has been added. The **nitrogen** inlet is briefly removed and 120 g. (1.5 moles) of **ammonium nitrate** is added; this discharges the chartreuse color. (*Caution: Vigorous foaming occurs.*) **Ethyl ether** (500 ml.) is added and the dry ice condenser is replaced by a standard water-cooled condenser. The **ammonia** is evaporated by allowing the stirred reaction mixture to warm to room temperature; this takes several hours and it is convenient to have it occur overnight.

Water (1.5 l.) is added and the mixture is transferred to a separatory funnel. The lower aqueous layer, which contains the **potassium salt of 3-acetyloxindole**, is separated and is then extracted with **ethyl ether** three times to remove a purple impurity. The aqueous layer is then made acidic to litmus by addition of **hydrochloric acid**; this causes precipitation of crude, tan-colored **3-acetyloxindole**. The mixture is chilled, and the product is collected by suction filtration and washed well on the filter with water. The yield of crude **3-acetyloxindole**, m.p. 204–206°, is 65–68 g. (74–78%). It may be purified by recrystallizing it from 1.7 l. of **chloroform** in the presence of 2 g. of **decolorizing carbon**. A heated filter funnel must be used in separating the **carbon** because the product starts to crystallize only slightly below the boiling point of **chloroform**. The recrystallized **3-acetyloxindole** weighs 53–59 g. (61–67%) and is in the form of white needles, m.p. 204–205.5°.

2. Notes

1. The *o*-acetoacetochloroanilide used was the technical product of Union Carbide Chemicals Co.; m.p. 107–109°.
2. If the reaction of **potassium** with liquid **ammonia** slows down before all the **potassium** is consumed, an additional pinch of **ferric nitrate hydrate** is added.

3. Discussion

3-Acetyloxindole has been made by condensing **ethyl acetate** with **oxindole** in the presence of **sodium ethoxide**³ and by heating **N-acetyloxindole** with **sodium amide** in **xylene**.⁴ The present method was developed by Hrutfiord and Bunnett.⁵ It illustrates a general principle for the synthesis of heterocyclic and homocyclic compounds. This principle involves the creation of an intermediate species that is of the **benzyne** type and has a nucleophilic center located so that it can add, intramolecularly, to the "triple bond" of the **benzyne** structure. Other applications of the principle using essentially the

present procedure are the conversion of thiobenz-*o*-bromoanilide or thiobenz-*m*-bromoanilide to 2-phenylbenzothiazole (90% and 68% respectively), of benz-*o*-chloroanilide to 2-phenylbenzoxazole (69%),⁵ of *o*-chlorohydrocinnamonitrile to 1-cyanobenzocyclobutene (61%),⁶ and of methanesulfone(N-methyl-*o*-chloro)anilide to 1-methyl-2,1-benzisothiazoline 2,2-dioxide (66%).⁷

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 5, 60](#)

References and Notes

1. University of North Caroline, Chapel Hill, North Carolina.
2. [M. Schlatter, *Org. Syntheses*, Coll. Vol. 3, 223 \(1955\).](#)
3. L. Horner, *Ann.*, **548**, 131 (1941).
4. H. Behringer and H. Weissauer, *Ber.*, **85**, 774 (1952).
5. J. F. Bunnett and B. F. Hrutfiord, *J. Am. Chem. Soc.*, **83**, 1691 (1961).
6. J. F. Bunnett and J. A. Skorcz, *J. Org. Chem.*, **27**, 3836 (1962).
7. J. F. Bunnett, T. Kato, R. R. Flynn, and J. A. Skorcz, *J. Org. Chem.*, **28**, 1 (1963).

Appendix

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

o-acetoacetochloroanilide

ethyl or isopropyl alcohol

thiobenz-*o*-bromoanilide

thiobenz-*m*-bromoanilide

benz-*o*-chloroanilide

methanesulfone(N-methyl-*o*-chloro)anilide

1-methyl-2,1-benzisothiazoline 2,2-dioxide

[hydrochloric acid \(7647-01-0\)](#)

[ammonia \(7664-41-7\)](#)

[benzyne \(71-43-2\)](#)

[ethyl acetate \(141-78-6\)](#)

[ethyl ether \(60-29-7\)](#)

[hydrogen \(1333-74-0\)](#)

chloroform (67-66-3)

nitrogen (7727-37-9)

decolorizing carbon,
carbon (7782-42-5)

isopropyl alcohol (67-63-0)

sodium ethoxide (141-52-6)

potassium (7440-09-7)

ammonium nitrate

xylene (106-42-3)

sodium amide (7782-92-5)

potassium amide

ferric nitrate hydrate

3-Acetyloxindole,
Oxindole, 3-acetyl- (17266-70-5)

oxindole (59-48-3)

2-phenylbenzothiazole (883-93-2)

2-phenylbenzoxazole (833-50-1)

1-Cyanobenzocyclobutene

N-acetyloxindole

o-chlorohydrocinnamonitrile (7315-17-5)

potassium salt of 3-acetyloxindole