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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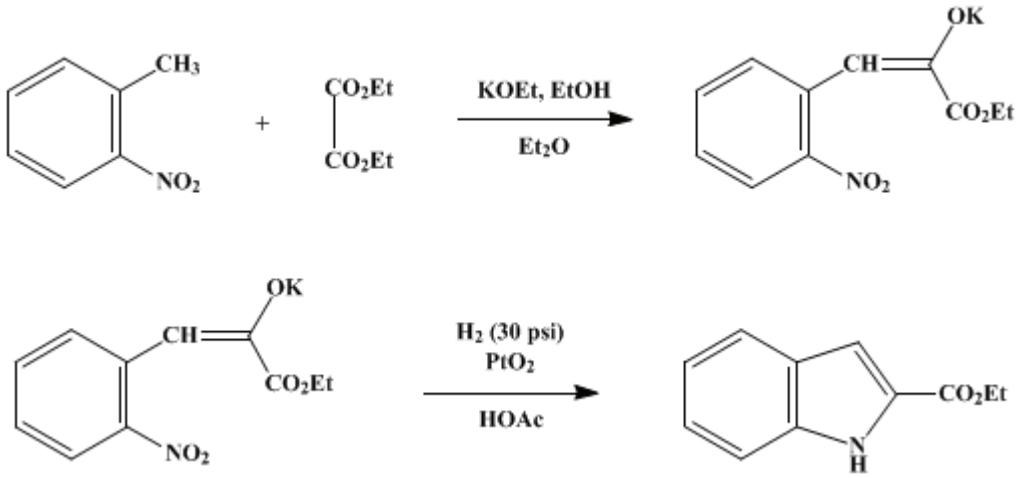
ETHYL INDOLE-2-CARBOXYLATE

[Indole-2-carboxylic acid, ethyl ester]



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Checked by E. J. Corey and Ronald J. McCaully.

1. Procedure

A. *Potassium salt of ethyl o-nitrophenylpyruvate*. Anhydrous ether (300 ml.) is placed in a 5-l., three-necked, round-bottomed flask fitted with a 500-ml. dropping funnel, a motor-driven stirrer (with seal), and a reflux condenser protected with a calcium chloride tube. Freshly cut potassium (39.1 g., 1.00 g. atom) is added. *Caution! Follow the precautions for handling potassium described in an earlier volume.*[2]

A slow stream of dry nitrogen is passed through the flask above the surface of the stirred liquid, and a mixture of 250 ml. of commercial absolute ethanol and 200 ml. of anhydrous ether is added from the dropping funnel just fast enough to maintain mild boiling. When all the potassium has dissolved (Note 1), the nitrogen is shut off. The solution is allowed to cool to room temperature, and 2.5 l. of anhydrous ether is added. Diethyl oxalate (146 g., 1.00 mole) is added with stirring, followed after 10 minutes by 137 g. (1.00 mole) of *o*-nitrotoluene. Stirring is discontinued after an additional 10 minutes, and the mixture is poured, with the aid of a connecting tube, into a 5-l. Erlenmeyer flask. The flask is stoppered and set aside for at least 24 hours. The lumpy deep-purple potassium salt of ethyl *o*-nitrophenylpyruvate is separated by filtration (Note 2) and washed with anhydrous ether until the filtrate remains colorless. The yield of the air-dried salt is 204–215 g. (74–78%).

B. *Ethyl indole-2-carboxylate*. Thirty grams (0.109 mole) of the potassium salt is placed in a 400-ml. hydrogenation bottle and dissolved by addition of 200 ml. of glacial acetic acid, producing a yellow, opaque solution (Note 3). Platinum catalyst[3] (0.20 g.) is added, the bottle is placed in a Parr low-pressure hydrogenation apparatus, and the system is flushed several times with hydrogen. With the initial reading on the pressure gauge about 30 p.s.i., the bottle is shaken until hydrogen uptake ceases and then for an additional 1–2 hours (Note 4). The catalyst is removed by filtration and washed with glacial acetic acid. The filtrate is placed in a 4-l. beaker, and 3 l. of water is added slowly with stirring. Ethyl indole-2-carboxylate precipitates as a yellow solid. It is separated by filtration, washed with five 100-ml. portions of water, and dried over calcium chloride in a desiccator. It weighs 13.2–13.6 g. (64–66%; 47–51% based on *o*-nitrotoluene); m.p. 118–124°.

The dried ether can be further purified by treatment with charcoal and recrystallization from a mixture of methylene chloride and light petroleum ether (b.p. 60–68°). This gives 11.3–11.7 g. (41–44% based on *o*-nitrotoluene) of ethyl indole-2-carboxylate in the form of white needles, m.p. 122.5–124°

(Note 5).

2. Notes

1. Complete solution of the potassium takes 1.5–2 hours with stirring and 2.5–3 hours without stirring.
2. Salt that sticks to the sides of the Erlenmeyer flask may be loosened with a piece of 10-mm. glass tubing that has not been fire-polished.
3. On addition of the acetic acid, a small amount of black solid settles out, but this dissolves when the solution is swirled for several minutes. The potassium salt of ethyl *o*-nitrophenylpyruvate, although it undergoes no apparent change in color, does not keep indefinitely in the dry state. After 3 weeks of storage at room temperature, the salt still produced a yellow solution when dissolved in acetic acid, but, after 3 months of storage, the dry salt produced a deep-red solution from which an oil, rather than crystalline ester, was obtained after catalytic hydrogenation.
4. The hydrogen pressure-drop corresponds to 0.325–0.335 mole (99–102%). When the hydrogen pressure drops below about 15 p.s.i., the hydrogen should be replenished in the reservoir tank to bring the pressure back up to about 30 p.s.i. The checkers found a reduction period of 4–6 hours sufficient; the submitters routinely used a 24-hour reduction period.
5. The reported melting points[4,5,6,7,8,9,10,11,12,13] range from 119°[6] to 125–126°.[7,8]

3. Discussion

The potassium salt of ethyl *o*-nitrophenylpyruvate is prepared essentially according to the method of Wislicenus and Thoma.[14] However, the isolation of ethyl *o*-nitrophenylpyruvate has been eliminated by liberating the ester from its potassium salt in the acetic acid used as solvent for the hydrogenation. Catalytic hydrogenation of the ester is carried out essentially by the procedure of Brehm.[5]

Ethyl *o*-nitrophenylpyruvate[4,14] and *o*-nitrophenylpyruvic acid[14,15,16,17,18,19,20,21] have been prepared by condensation of *o*-nitrotoluene with diethyl oxalate in the presence of potassium ethoxide,[4,14] sodium ethoxide,[15,16,17,18,19,20] or sodium methoxide.[21] Sodium ethoxide is less reactive, however, and cannot be substituted successfully for potassium ethoxide in the present procedure, as it gives a very poor yield and poor quality of precipitated sodium salt. With sodium ethoxide the reaction does not appear to go to completion even under the conditions of refluxing ethanol usually employed,[15,16,17,18,19,20,21] which are considerably more severe than the room temperature conditions employed with potassium ethoxide in the present procedure. *o*-Nitrophenylpyruvic acid has also been prepared by hydrochloric acid hydrolysis of *o*-nitro-α-acetaminocinnamic azlactone.[4]

Ethyl indole-2-carboxylate[5,13] and the corresponding carboxylic acid[4,17,19,22,23] have been prepared by reductive cyclization of ethyl *o*-nitrophenylpyruvate and *o*-nitrophenylpyruvic acid, both in the presence of reducing agents such as zinc and acetic acid,[4,13] ferrous sulfate and ammonium hydroxide,[17,19,23] and sodium hydrosulfite,[17,22] and by platinum-catalyzed hydrogenation.[5] The ethyl ester has also been prepared by esterification[9,19] of the acid in the presence of sulfuric[6] and hydrochloric[12] acid catalysts, by the Fischer indole synthesis from ethyl pyruvate phenylhydrazone catalyzed by polyphosphoric acid,[11] sulfuric acid and acetic acid,[11,17] or zinc chloride,[24,25,26] and by stannous chloride reduction of ethyl 1-hydroxyindole-2-carboxylate.[7] Indole-2-carboxylic acid has also been prepared by the Fischer indole synthesis from pyruvic acid phenylhydrazone catalyzed by zinc chloride,[24] by the Madelung synthesis from potassium oxalyl-*o*-toluidine,[27] by zinc and acetic acid reduction of 1-hydroxy- and 1-methoxyindole-2-carboxylic acids,[28] by cyclizative demethanolation of *o*-amino-α-methoxycinnamic acid,[29] by reductive cyclization and hydrolysis of *o*-nitrobenzalrhodanine,[12] by alkaline hydrolysis and decarboxylation of dimethyl indole-2,3-dicarboxylate,[30] and by fusion of 2-methylindole with potassium hydroxide in the presence of air.[31]

4. Merits of the Preparation

The procedure employs the least expensive commercially available starting materials and requires the minimum number of reaction steps.

Alkaline hydrolysis of ethyl indole-2-carboxylate yields indole-2-carboxylic acid,[4,5,7,11,24,25] which

can be decarboxylated to indole by heating at 230°.[24,25] The acid or its ester serves as a readily accessible indole capable of electrophilic substitution at the 3-position,[6,22] and as a precursor for the synthesis of indole-2-acylamino derivatives of interest as model compounds in the study of alkaloid synthesis[5,23,32] and as a degradation product of the mold metabolite, gliotoxin.[4,33,34,35] Reduction of the ester with lithium aluminum hydride yields indole-2-methanol,[5] which can be oxidized to indole-2-carboxaldehyde by potassium permanganate in acetone.[10] Reduction of the acid chloride with lithium aluminum tri-*tert*-butoxy hydride[36] is a convenient synthesis of indole-2-carboxaldehyde.[37]

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Appendix

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

polyphosphoric acid

Potassium salt of ethyl o-nitrophenylpyruvate

o-nitro-α-acetaminocinnamic azlactone

potassium oxalyl-o-toluidine

lithium aluminum tri-tert-butoxy hydride

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

hydrogen (1333-74-0)

potassium permanganate (7722-64-7)

nitrogen (7727-37-9)

sodium hydrosulfite (7775-14-6)

stannous chloride

ferrous sulfate (13463-43-9)

platinum (7440-06-4)

acetone (67-64-1)

sodium methoxide (124-41-4)

potassium hydroxide (1310-58-3)

zinc (7440-66-6)

sodium ethoxide (141-52-6)

zinc chloride (7646-85-7)

ammonium hydroxide (1336-21-6)

potassium (7440-09-7)

methylene chloride (75-09-2)

o-nitrotoluene (88-72-2)

potassium ethoxide (917-58-8)

lithium aluminum hydride (16853-85-3)

Indole (120-72-9)

indole-2-carboxylic acid (1477-50-5)

2-Methylindole (95-20-5)

diethyl oxalate (95-92-1)

Ethyl indole-2-carboxylate,
Indole-2-carboxylic acid, ethyl ester (3770-50-1)

ethyl o-nitrophenylpyruvate

ethyl pyruvate phenylhydrazone

ethyl 1-hydroxyindole-2-carboxylate

pyruvic acid phenylhydrazone

dimethyl indole-2,3-dicarboxylate (54781-93-0)

indole-2-methanol

indole-2-carboxaldehyde

o-nitrophenylpyruvic acid (5461-32-5)

o-amino-α-methoxycinnamic acid

o-nitrobenzalrhodanine