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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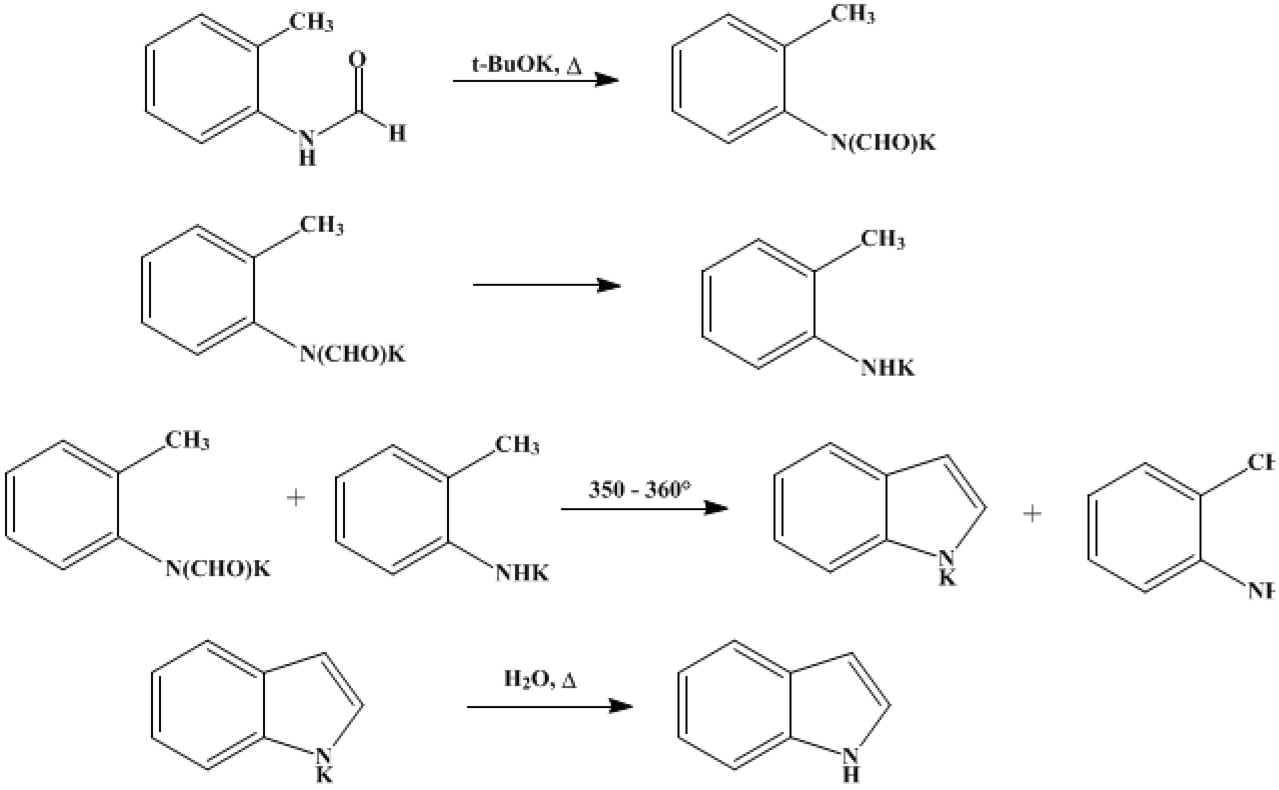
INDOLE



Submitted by F. T. Tyson
Checked by R. L. Shriner and C. H. Tilford.

1. Procedure

A 2-l. three-necked round-bottomed flask is fitted with a reflux condenser and a glass inlet tube connected to a cylinder of nitrogen. The third opening of the flask is closed by a stopper. The top of the condenser is connected to an air trap which consists of two 500-ml. suction flasks joined in series. The first suction flask is empty; the second contains 100 ml. of paraffin oil, and the inlet tube of this flask extends slightly below the surface of the oil.

In the reaction flask is placed 600 ml. of commercial *tert*-butyl alcohol (Note 1), and the air in the flask is displaced by dry nitrogen gas. Then 29 g. (0.75 gram atom) of metallic potassium is added, in portions, to the alcohol. The mixture is heated on a water bath until all the potassium has dissolved, and then 68 g. (0.5 mole) of *o*-formotoluide (Note 2) is added and brought into solution. The condenser is set for distillation with a filter flask as the receiver; this flask is protected from the air by connecting it to the trap used in the initial operation. The reaction flask is surrounded by a metal bath, and the excess alcohol is removed by distillation. The residue is heated to 350–360° for about 20 minutes (Note 3) and then is allowed to cool in a stream of nitrogen. The residue is decomposed by addition of 300 ml. of water, and the mixture is steam-distilled to remove the indole. The distillate is extracted successively with 300 ml. and 100 ml. of ether, and the combined ether extracts are shaken with cold dilute 5% hydrochloric acid to remove small amounts of *o*-toluidine. The ether extract is washed with 100 ml. of water, followed by 100 ml. of 5% sodium carbonate solution, and is dried over 20 g. of sodium sulfate. The ether is removed by distillation, and the residue is distilled under reduced pressure. Indole distils at 142–144°/27 mm. (128°/10 mm.; 121°/5 mm.) as a pale yellow oil which solidifies and then melts at 52–53°. The yield is 23 g. (79%) (Note 4).

2. Notes

1. Alcohols other than *tert*-butyl alcohol, such as methyl, ethyl, butyl, or isobutyl alcohol, may be used, but with a decrease in yield. If methyl or ethyl alcohol is substituted for *tert*-butyl alcohol, the potassium should be added in smaller portions and the more vigorous reaction must be controlled by external cooling. Furthermore, if methyl alcohol is used the amount of potassium should be decreased from 0.75 gram atom to 0.5 gram atom.
2. *o*-Formotoluide can be prepared by heating a mixture of 856 g. (8 moles) of *o*-toluidine and 403 g. (8.4 moles) of 90% formic acid on a steam bath for about 3 hours and allowing the reaction mixture to stand overnight. The mixture is fractionated under reduced pressure; there is obtained 920–963 g. (85–89%) of *o*-formotoluide, b.p. 173–5°/25 mm., m.p. 55–58°. This product is a pale yellow solid which contains traces of toluidine and possesses an odor indicating the presence of traces of an isocyanide. However, the material is sufficiently pure for conversion to indole. By use of 99% formic acid, a quantitative yield may be obtained. If a purer product is desired, the original reaction mixture is mixed with about a liter of water, the crude formotoluide is filtered, then washed with 1% hydrochloric acid and with water. After drying, the crude formotoluide is recrystallized from benzene-petroleum ether. The yield is practically the same as that obtained by direct distillation, and the product melts at 61°. In order to assure freedom from moisture, the recrystallized product may be distilled under reduced pressure; the loss in this distillation is negligible.
3. During this interval combustible gases, chiefly carbon monoxide and hydrogen, are evolved, and a liquid, which is principally *o*-toluidine, distils.
4. The product is pale yellow. The color may be removed by crystallizing the material from a mixture of 100 ml. of petroleum ether and about 10 ml. of ethyl ether. The recovery is 21 g. (91%).

3. Discussion

Indole has been obtained through many syntheses which have little value as methods of preparation. In addition to these syntheses it has been prepared by heating 2-amino-ω-chlorostyrene with sodium methoxide;[1] by pyrolysis of 2,2'-diaminostilbene hydrochloride under reduced pressure;[2] by reduction of indoxyl with zinc dust and alkali;[3] by reduction of 2-aminoindole with sodium and alcohol;[4] by reduction of methyl *o*-nitrostyrylcarbamate,[5] by heating *o*-formylphenylglycine with acetic anhydride and sodium acetate;[6] by passing a mixture of acetylene and aniline through an iron tube at 700°;[7] and by reduction of ω,2-dinitrostyrene with iron and acetic acid.[8] The method described above is related to the Madelung synthesis of 2-alkylindoles[9] and has been published.[10] The methods for preparation of indole have been examined experimentally.[11] The authors recommend the method of Reissert,[12] which involves condensation of *o*-nitrotoluene with ethyl oxalate, followed by reduction to indole-2-carboxylic acid and decarboxylation of the latter. A patent reports the preparation of indole by catalytic dehydrogenation of *o*-ethylaniline at 650° in the presence of titania gel.[13] The cyclization of N-formyl-*o*-toluidine with sodium in methanol has been described and is recommended as a safer and less expensive method than that involving the use of potassium metal.[14]

The reaction of carbon monoxide with *o*-toluidine, as the sodium salt, under pressure, at an elevated temperature, has been patented.[15]

References and Notes

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

petroleum ether

benzene-petroleum ether

methyl or ethyl alcohol

methyl, ethyl, butyl, or isobutyl alcohol

indoxyl

ω,2-dinitrostyrene

titania gel

acetylene (74-86-2)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methyl alcohol,
methanol (67-56-1)

ether,
ethyl ether (60-29-7)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

aniline (62-53-3)

hydrogen (1333-74-0)

carbon monoxide (630-08-0)

iron (7439-89-6)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

formic acid (64-18-6)

nitrogen (7727-37-9)

isocyanide (57-12-5)

sodium methoxide (124-41-4)

zinc (7440-66-6)

sodium (13966-32-0)

potassium (7440-09-7)

Ethyl oxalate

o-nitrotoluene (88-72-2)

Indole (120-72-9)

toluidine (106-49-0)

formotoluide (3085-54-9)

2-amino-ω-chlorostyrene

2-aminoindole

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

tert-butyl alcohol (75-65-0)

o-toluidine (95-53-4)

o-formotoluide,
N-formyl-o-toluidine (94-69-9)

methyl o-nitrostyrylcarbamate

o-formylphenylglycine

o-ethylaniline (578-54-1)

2,2'-diaminostilbene hydrochloride