



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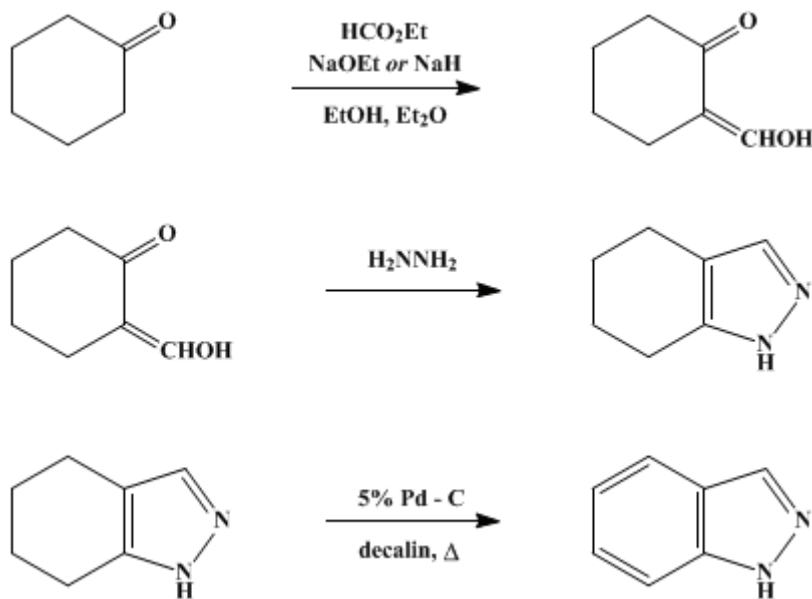
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 4, p.536 (1963); Vol. 39, p.27 (1959).

INDAZOLE

[1H-Indazole]



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1. Procedure

A. *2-Hydroxymethylcyclohexanone, Method 1.* A mixture of 23 g. (1 g. atom) of sodium metal cut in approximately 1-cm. cubes, 2 l. of dry ether, 98 g. (103 ml., 1 mole) of redistilled cyclohexanone, and 110 g. (120 ml., 1.5 moles) of ethyl formate is placed in a 5-l. three-necked flask equipped with a stirrer, stopper, and vent tube. The reaction is initiated by the addition of 5 ml. of ethyl alcohol to the stirred mixture, which is then placed in a cold water bath. Stirring is continued for 6 hours. After standing overnight, 25 ml. of ethyl alcohol is added, and the mixture is stirred for an additional hour. After the addition of 200 ml. of water, the mixture is shaken in a 3-l. separatory funnel. The ether layer is washed with 50 ml. of water, and the combined aqueous extracts are washed with 100 ml. of ether. The aqueous layer is acidified with 165 ml. of 6*N* hydrochloric acid, and the mixture is extracted twice with 300 ml. of ether. The ether solution is washed with 25 ml. of saturated sodium chloride solution and then is dried by the addition of approximately 30 g. of anhydrous magnesium sulfate powder. The drying agent is removed by suction filtration, and the ether is evaporated on the steam bath. The residue is distilled under reduced pressure using a 6-inch Vigreux column. After a small fore-run there is obtained 88–94 g. (70–74%) of 2-hydroxymethylcyclohexanone, b.p. 70–72°/5 mm., n_D^{25} 1.5110 (Note 1).

2-Hydroxymethylcyclohexanone, Method 2. A mixture of 50 g. (1 mole) of 48% sodium hydride dispersed in mineral oil (Note 2), 2 l. of dry ether, and 5 ml. of ethyl alcohol is placed in a 5-l. three-necked flask equipped with a stirrer, dropping funnel, and vent tube. The reaction vessel is cooled by means of a cold water bath, and a solution of 98 g. (103 ml., 1 mole) of redistilled cyclohexanone and 110 g. (120 ml., 1.5 moles) of ethyl formate is added dropwise during 1 hour. Stirring is continued for 6 hours (Note 3), and the solution is allowed to stand overnight. After the addition of 20 ml. of ethyl alcohol, the mixture is stirred for 1 hour. Water (200 ml.) is added to the flask with stirring, the mixture is shaken in a 3-l. separatory funnel and the organic layer separated. The product is isolated according to the procedure described in Method 1. The yield of 2-hydroxymethylcyclohexanone is the same by both methods.

B. *4,5,6,7-Tetrahydroindazole*. A solution of 63 g. (0.5 mole) of *2-hydroxymethylenecyclohexanone* and 500 ml. of *methyl alcohol* contained in a 2-l. beaker is treated with 25 ml. (0.5 mole) of *hydrazine hydrate* in small portions (Note 4). After standing for 30 minutes the mixture is concentrated by warming under reduced pressure on the steam bath. To aid in removing the water, 100 ml. of *ethyl alcohol* is added, and again the mixture is concentrated by heating under reduced pressure. The residue is dissolved in about 100 ml. of hot petroleum ether (Note 5), and after cooling in an ice bath for 1 hour the solid that separates is collected by suction filtration and washed with a small amount of cold petroleum ether. The crude *4,5,6,7-tetrahydroindazole*, m.p. 79–80°, weighs 58–60 g. (95–98%) and is sufficiently pure to be used in the next step (Note 6) and (Note 7).

C. *Indazole*. A mixture of 50 g. (0.41 mole) of *4,5,6,7-tetrahydroindazole*, 35 g. of 5% *palladium on carbon* (Note 8) and 1 l. of dry *decalin* is placed in a 3-l. round-bottomed flask and heated under reflux for 24 hours. The hot mixture is filtered by suction, using a previously heated Büchner funnel, and the filtrate is allowed to cool. After standing overnight, the *indazole* that separates is collected by suction filtration, washed with 100 ml. of petroleum ether, and air-dried. The solid is dissolved in 750 ml. of hot *benzene*, and about 4 g. of *decolorizing carbon* is added. The mixture is filtered through a fluted filter paper and then is refiltered, using the same filter paper. Two liters of warm petroleum ether is added, and the solution is cooled in an ice bath for 2 hours. The *indazole* (m.p. 146–147°) is collected by suction filtration and after air drying weighs 24–25 g. (50–52%).

2. Notes

1. *2-Hydroxymethylenecyclohexanone* begins to polymerize after standing at room temperature for several days.
2. Available from Metal Hydrides Inc., Beverly, Massachusetts.
3. After an hour or so, the ether comes to a boil, and the reaction mixture is cooled in a cold water bath.
4. The reaction is exothermic but is contained in the beaker.
5. The petroleum ether fraction used was Skellysolve B (boiling range 60–70°).
6. *4,5,6,7-Tetrahydroindazole* can be distilled, b.p. 135–140°/5 mm. It is recrystallized from petroleum ether and melts at 84°.
7. The petroleum ether purification step may be eliminated with equally satisfactory results. After dehydration with *ethyl alcohol*, the residue is dried under reduced pressure to constant weight and used directly for the next step.
8. The *palladium* catalyst is prepared according to *Organic Syntheses Coll. Vol. 3*, 686 (1955). It can be reused for the dehydrogenation of *4,5,6,7-tetrahydroindazole* to *indazole*. The yield is somewhat better with used catalyst than with fresh catalyst.

3. Discussion

2-Hydroxymethylenecyclohexanone has been prepared by the reaction of *cyclohexanone* and alkyl formates.^{2,3,4}

4,5,6,7-Tetrahydroindazole has been prepared by the hydrolysis of *1-carbamyl-4,5,6,7-tetrahydroindazole*.^{2,3} It was first prepared in the Lilly Research Laboratories by Dr. N. Easton by the reaction of *2-hydroxymethylenecyclohexanone* and *hydrazine hydrate*.

Indazole has been prepared according to the method reported in *Organic Syntheses*.⁵ Recently, *indazole* has been prepared by the hydrolysis or reduction of *3-cyanoindazole*,⁶ by heating *1-o-tolyl-3,3-dimethyltriazine*,⁷ by the coupling of *N-nitroso-o-benzo-(or aceto-)toluidide*,^{8,9,10} and by the decomposition of *cis-2-stilbenediazonium fluoroborate*.¹¹ The present method employs milder reaction conditions.¹²

This preparation is referenced from:

- *Org. Syn. Coll. Vol. 5*, 650
- *Org. Syn. Coll. Vol. 6*, 389
- *Org. Syn. Coll. Vol. 6*, 590

References and Notes

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 12. Ainsworth, *J. Am. Chem. Soc.*, **79**, 5242 (1957).
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Appendix Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

petroleum ether

N-nitroso-o-benzo-(or aceto-)toluidide

ethyl alcohol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methyl alcohol (67-56-1)

ether (60-29-7)

Cyclohexanone (108-94-1)

sodium chloride (7647-14-5)

decolorizing carbon (7782-42-5)

sodium (13966-32-0)

palladium,
palladium on carbon (7440-05-3)

hydrazine hydrate (7803-57-8)

ethyl formate (109-94-4)

magnesium sulfate (7487-88-9)

sodium hydride (7646-69-7)

Indazole,
1H-Indazole (271-44-3)

2-Hydroxymethylenecyclohexanone (823-45-0)

4,5,6,7-Tetrahydroindazole (2305-79-5)

decalin (91-17-8)

1-carbamyl-4,5,6,7-tetrahydroindazole

3-cyanoindazole

1-o-tolyl-3,3-dimethyltriazine

cis-2-stilbenediazonium fluoroborate