Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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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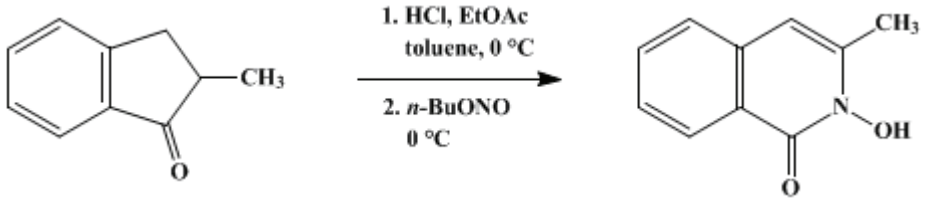
2-HYDROXY-3-METHYLISOCARBOSTYRIL

[Isocarbostyril, 2-hydroxy-3-methyl-]



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1. Procedure

A solution of 8.0 g. (7.5 ml., 0.055 mole) of 2-methyl-1-indanone (Note 1) in 100 ml. of toluene is prepared in a 500-ml., three-necked, round-bottomed flask equipped with a thermometer, a dropping funnel, and a magnetic stirrer. The flask is immersed in a freezing mixture of sodium chloride and ice. When the solution temperature reaches 0°, 70 ml. (0.21 mole) of 3*N* hydrochloric acid in ethyl acetate (Note 2) is added slowly (Note 3). To this mixture 8.0 ml. (0.068 mole) of freshly prepared *n*-butyl nitrite (Note 4) in 25 ml. of toluene is added with stirring over a 10-minute period (Note 5). The mixture is stirred for 1 hour at 0° and for an additional hour at room temperature. The two layers are separated, and the upper layer (toluene) is concentrated to one-half volume. Both solutions are refrigerated at −20° for 4 days. The precipitated orange product is collected by filtration from each layer. Further concentration of each filtrate under reduced pressure to one-half volume gives additional crude product (Note 6).

The various fractions are combined, washed with 20 ml. of cold ether, and dried. Recrystallization from methylene chloride-ether (Note 7) gives 6.0–6.6 g. (62–69%) of 2-hydroxy-3-methylisocarbostyril as light orange plates, m.p. 175–180°. Sublimation of this material at 100–110° (0.5 mm.) gives a white product, m.p. 182–184°, with softening at 174° (Note 7).

2. Notes

1. The 2-methyl-1-indanone, b.p. 65–66° (0.6 mm.) [lit.[2] b.p. 120° (15 mm.)], was prepared by the following method, described by Colonge and Weinstein.[2]
To 15.0 g. (0.50 mole) of paraformaldehyde (Eastman Organic Chemicals) and 100 g. (0.75 mole) of propiophenone (Eastman Organic Chemicals) in a 250-ml. Erlenmeyer flask, 10 ml. of 1*N* alcoholic potassium hydroxide solution was added with stirring. After a few minutes a clear solution formed, and the temperature rose to 35° and then fell slowly. The yellow solution was stirred for 5.5 hours at room temperature, during which time the solution became turbid. The turbid solution was poured into 150 ml. of water, and the mixture was acidified with concentrated hydrochloric acid (Congo red indicator).
The mixture was extracted with two 150-ml. portions of benzene, and the combined organic extracts were washed with two 150-ml. portions of water, two 150-ml. portions of 10% aqueous sodium carbonate, and two 150-ml. portions of water. The benzene extracts were dried over anhydrous sodium sulfate, and the solvent was removed. The yellow residue was distilled under reduced pressure to give a forerun consisting of 45 g. (0.34 mole) of unconsumed propiophenone followed by 32–36 g. (39–44%) of 3-hydroxy-2-methylpropiophenone, b.p. 108–110° (0.55 mm.) [lit.[2] b.p. 158–162° (17 mm.)]; infrared band (neat) at 5.94 μ (C=O).
3-Hydroxy-2-methylpropiophenone (30 g., 0.183 mole) was added slowly to 150 ml. of concentrated sulfuric acid with stirring. The temperature rose and the solution turned dark brown. The temperature remained at 80° for 10 minutes and then slowly fell. After 1 hour the dark solution was poured onto 200 g. of cracked ice. The mixture was extracted with two 100-ml. portions of ether. The ethereal solution

was washed with two 100-ml. portions of water, two 100-ml. portions of saturated aqueous sodium bicarbonate, and again with two 100-ml. portions of water. It was dried over anhydrous potassium carbonate, and the solvent was removed. The residue was distilled to give 18–19 g. (67–71%) of a pale yellow liquid, b.p. 65–66° (0.6 mm.) [lit[2]. b.p. 120° (15 mm.)], n^{20}20D 1.5510 (lit.[2] n^{23}D 1.5511); infrared band (neat) at 5.80 μ (C=O).

2. Prepared by dissolving 17.5 ml. of 12*N* hydrochloric acid in 52.5 ml. of ethyl acetate.

3. Two phases are obtained; this heterogenous mixture is vigorously stirred during the addition of *n*-butyl nitrite.

4. The *n*-butyl nitrite must be refrigerated after preparation[3] and used as soon as possible thereafter. The use of commercially available *n*-butyl nitrite invariably led to lower yields of the isocarbostyril.

5. With lower hydrochloric acid concentration and reversal of the mode of addition, *i.e.*, acid to indanone-nitrite mixture, the intermediate 2-methyl-2-nitroso-1-indanone may also be isolated as its dimer. This can be isomerized to the isocarbostyril rapidly in refluxing methanolic sodium methoxide and more slowly in concentrated hydrochloric acid.[4]

6. To determine whether all the isocarbostyril has been isolated from the filtrates, a small aliquot of the filtrate is treated with excess aqueous ferric chloride. The appearance of a deep purple color indicates the necessity for further concentration under reduced pressure and precipitation of product.

7. The checkers used methylene chloride alone as the solvent for recrystallization; sublimation gave a product, m.p. 178–180°.

3. Discussion

2-Hydroxy-3-methylisocarbostyril has been prepared by the present method,[4] and in 12–15% yield by the ozonization of 3-methylisoquinoline-2-oxide.[5]

4. Merits of the Preparation

This simple, one-step ring expansion is the only available method for the preparation of 2-hydroxy-3-alkylisocarbostyrils in good yield from the corresponding 2-alkyl-1-indanones. Table I lists five new hydroxyisocarbostyrils prepared in this manner.

TABLE I SYNTHESES OF 2-HYDROXY-3-ALKYLISOCARBOSTYRILS

2-Alkyl Substituent	Yield, %	M.P., °C
Ethyl	65	154–155
Propyl	64	139–141
Isopropyl	49	107–108
Butyl	45	108–109
t-Butyl	20	104–106

Direct reduction of the 2-hydroxy-3-alkylisocarbostyrils gives 3-alkylisocarbostyrils and provides a useful synthesis of these compounds.

References and Notes

1. Contribution No. 842 from the Department of Chemistry, Fordham University, New York, N. Y. 10458. This work was supported by the Directorate of Chemical Sciences, Air Force Office of Scientific Research, under Grant AF-AFOSR-62-18 and 488-64.
2. J. Colonge and G. Weinstein, *Bull. Soc. Chim. France*, [5] **19**, 462 (1952).
3. W. A. Noyes, *Org. Syntheses*, Coll. Vol. **2**, 108 (1943).
4. E. J. Moriconi, F. J. Creegan, C. K. Donovan, and F. A. Spano, *J. Org. Chem.*, **28**, 2215 (1963); E. J. Moriconi and F. J. Creegan, *J. Org. Chem.*, **31**, 2090 (1966).

5. E. J. Moriconi and F. A. Spano, *J. Am. Chem. Soc.*, **86**, 38 (1964).

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

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

sodium methoxide (124-41-4)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

ferric chloride (7705-08-0)

n-butyl nitrite (544-16-1)

methylene chloride (75-09-2)

Propiophenone (93-55-0)

2-Hydroxy-3-methylisocarbostyril,
Isocarbostyril, 2-hydroxy-3-methyl- (7114-79-6)

2-methyl-1-indanone (17496-14-9)

3-hydroxy-2-methylpropiophenone (3338-15-6)

2-methyl-2-nitroso-1-indanone

3-methylisoquinoline-2-oxide

paraformaldehyde (30525-89-4)