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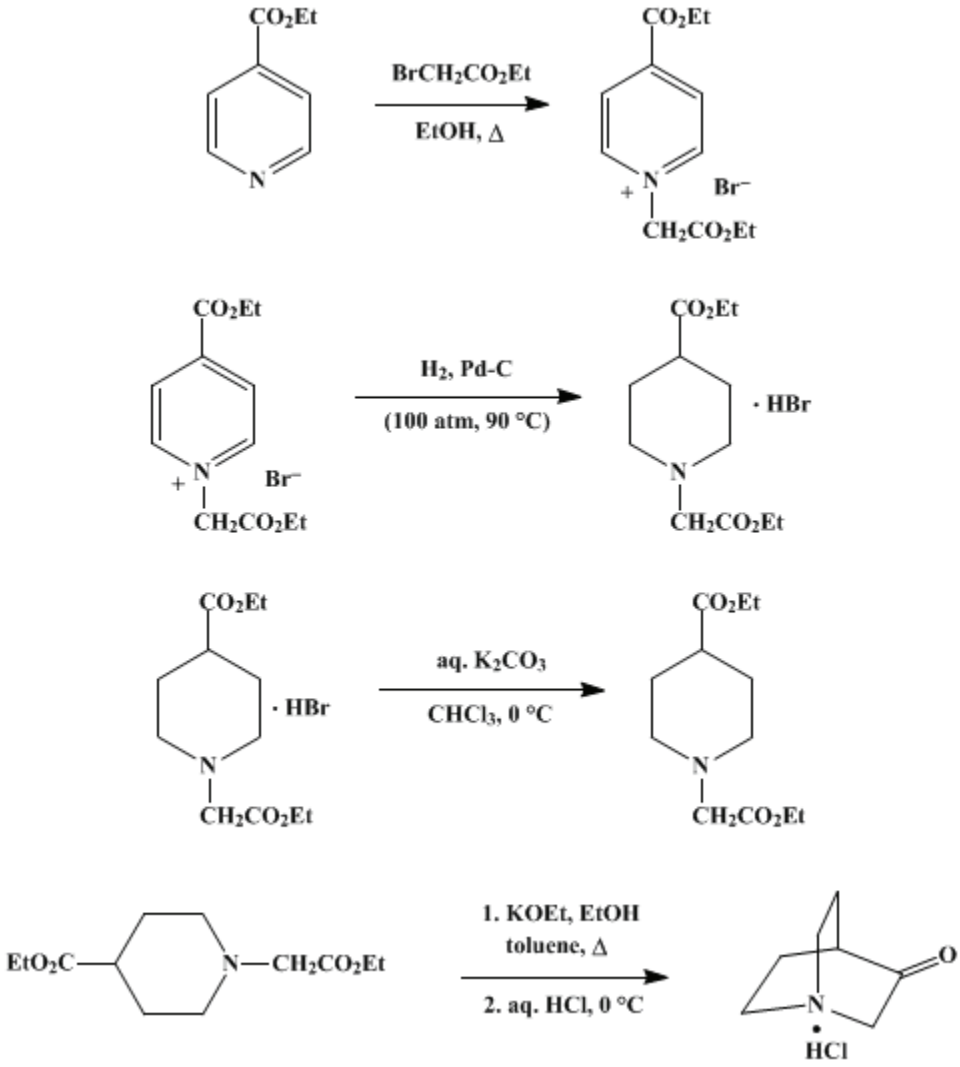
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.044.0086

Organic Syntheses, Coll. Vol. 5, p.989 (1973); Vol. 44, p.86 (1964).

3-QUINUCLIDONE HYDROCHLORIDE

[3-Quinuclidinone, hydrochloride]



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1. Procedure

A. *1-Carbethoxymethyl-4-carbethoxypyridinium bromide*. A solution of 151 g. (1.00 mole) of ethyl isonicotinate (Note 1) and 167 g. (1.00 mole) of ethyl bromoacetate in 500 ml. of ethanol is allowed to stand overnight at room temperature in a 1-l. round-bottomed flask equipped with a reflux condenser (Note 2). The mixture is then heated at the reflux temperature for 4 hours. The resulting solution of 1-carbethoxymethyl-4-carbethoxypyridinium bromide is used directly for the next step (Note 3).

B. *1-Carbethoxymethyl-4-carbethoxypiperidine*. Fifteen grams of 10% palladium on charcoal[2] is added to the solution of the pyridinium bromide. The mixture is placed in an agitated 2-l. hydrogenation autoclave and hydrogenated at 90° under an initial pressure of 100 atm. (Note 4). Slightly more than the calculated amount of hydrogen (3 moles) is absorbed within 30–60 minutes. The mixture is cooled to 25°, and the catalyst is separated by filtration and washed with 100 ml. of ethanol. The filtrate is evaporated to dryness under water-aspirator vacuum at a bath temperature of 50–60°. The residue,

semicrystalline 1-carbethoxymethyl-4-carbethoxypiperidine hydrobromide, is taken up in 500 ml. of ice-cold water. The solution is added to 500 ml. of chloroform in a 5-l. beaker immersed in an ice bath, and an ice-cold solution of 150 g. of potassium carbonate in 250 ml. of water is added gradually with stirring (Note 5). After the carbon dioxide evolution has subsided, the mixture is placed in a 2-l. separatory funnel and thoroughly shaken for some time. The lower, organic layer is drawn off and washed once with 200 ml. of water. The aqueous layers are combined and washed once with 500 ml. of chloroform. The two chloroform extracts are combined and dried over anhydrous sodium sulfate. After 1 hour the sodium sulfate is separated on a Büchner funnel and washed with two 200-ml. portions of chloroform. The chloroform is removed on a steam bath, and the resulting oily residue is distilled under high vacuum through a 20-cm. Vigreux column. A fore-run, weight 4–8 g., is collected below 110° (0.20 mm.). Then 156–190 g. (64–78%) of 1-carbethoxymethyl-4-carbethoxypiperidine is collected as a colorless oil, b.p. 111–113° (0.2 mm.), d15/15 1.057, n^{20}D 1.4585.

C. *3-Quinuclidone hydrochloride.* A 2-l. three-necked flask is fitted with a Hershberg stirrer, a pressure-equalizing addition funnel, and a condenser connected to a source of dry nitrogen. Absolute toluene (330 ml.) and 80 g. (2.05 g. atom) of potassium free of oxide crust are added. *(Caution! Directions[3] for the safe handling of potassium should be consulted.)* The air in the flask is replaced by an atmosphere of dry nitrogen that is maintained until the reaction mixture is decomposed. The flask is heated in an oil bath until the toluene begins to reflux gently. As soon as the potassium is molten, it is pulverized by vigorous stirring. One hundred twenty-five milliliters (98.6 g., 2.14 moles) of absolute ethanol (Note 6) is added through the addition funnel within 30 minutes while heating and stirring are continued. After disappearance of the potassium the temperature is raised to 130°, and a solution of 200 g. (0.822 mole) of 1-carbethoxymethyl-4-carbethoxypiperidine in 500 ml. of absolute toluene is added within 2 hours. The mixture is stirred and heated for an additional 3 hours.

The resulting solution is cooled to 0° and decomposed by careful addition of 500 ml. of 10*N* hydrochloric acid. The mixture is transferred to a separatory funnel, the aqueous phase is separated, and the toluene layer is extracted with two 250-ml. portions of 10*N* hydrochloric acid. The aqueous extracts are combined and heated under reflux for 15 hours to effect decarboxylation. The hot, dark-colored solution is treated with 10 g. of activated charcoal, filtered, and evaporated to dryness under reduced pressure. The residue is washed into a separatory funnel with 300 ml. of water. The solution is treated with saturated aqueous potassium carbonate solution until it is alkaline to litmus; the carbonate solution must be added very carefully to prevent excessive foaming. Solid potassium carbonate is added until a thin slurry is obtained, and the slurry is extracted with four 400-ml. portions of ether. The combined ether extracts are dried for at least 60 minutes over calcined potassium carbonate and then filtered.

The ether is removed by distillation on a steam bath through a column filled with Raschig rings. The yellowish crystalline residue is treated with 150 g. of ice and 150 g. (130 ml.) of 10*N* hydrochloric acid, and the solution is evaporated to dryness under reduced pressure (Note 7). The crystalline residue is dissolved in the minimum amount of hot water (about 70 ml.), and boiling isopropyl alcohol (about 1.5 l.) is added until crystalline 3-quinuclidone hydrochloride begins to separate. The mixture is cooled to 0–5°, and the solid is separated by filtration, washed with acetone, and dried. The yield of 3-quinuclidone hydrochloride, m.p. 294–296° (sealed capillary) (Note 8), is 102–109 g. (77–82%).

2. Notes

1. The checkers used ethyl isonicotinate purchased from K and K Laboratories, Inc., Jamaica, New York, or prepared by esterification of isonicotinic acid as described by La Forge[4] for nicotinic acid.
2. The quaternization is slightly exothermic.
3. The quaternary salt may be isolated by evaporation of the solution and subsequent recrystallization of the residue from isopropyl alcohol; m.p. 159° (dec.). Calcd. for $C_{12}H_{16}BrNO_4$: C, 45.30; H, 5.07; Br, 25.12. Found: C, 45.41; H, 5.14; Br, 25.28.
4. The checkers found that hydrogenation proceeded rapidly and quite exothermically at a pressure of only 7 atm. at 90°. They used 10% palladium-on-carbon powder purchased from Engelhard Industries Inc., Newark, New Jersey.
5. The evolution of carbon dioxide causes considerable foaming. Losses are easily avoided if a 5-l. beaker is used.

6. Commercial absolute alcohol was further dried by treatment with magnesium and a little iodine with subsequent redistillation, as described by Lund and Bjerrum.[5]
7. In an alternative method of isolating crude quinuclidone hydrochloride, found by the checkers to give equally good results, the dried ether solution of quinuclidone is transferred to a 2-l. round-bottomed flask equipped with a stirrer, a gas-inlet tube, and a gas-exit tube. The flask is immersed in an ice bath, and gaseous hydrogen chloride is passed into the stirred solution until it begins to bubble out, indicating that the solution is saturated. The quinuclidone hydrochloride that precipitates is collected on a Büchner funnel, washed with acetone, and dried in a vacuum desiccator. The product is then dissolved in hot water and precipitated with isopropyl alcohol as described in the procedure.
8. The melting point depends on the rate of heating and the apparatus used. The checkers observed m.p. 297–305°, 298–303°, and 301° under various conditions.

3. Discussion

Quinuclidone hydrochloride has been prepared by intramolecular condensation of 1-carbethoxymethyl-4-carbethoxypiperidine with potassium[6,7,8] or, as in the present procedure, with potassium ethoxide.[9] 1-Carbethoxymethyl-4-carbethoxypiperidine has been prepared by alkylating ethyl hexahydroisonicotinate with ethyl chloroacetate[6,8] or by the present method.[7]

4. Merits of the Preparation

This is the most convenient way to prepare quinuclidone hydrochloride. The second step illustrates the conversion of an N-alkylpyridinium salt to an N-alkylpiperidine. The third step illustrates the formation of a bicyclic system by the Dieckmann condensation.

Quinuclidone can be reduced to quinuclidine.[6] Depending on the availability of starting materials, either this reduction or the dehydrative cyclization of 4-(2-hydroxyethyl)piperidine[10] is the most convenient synthesis of quinuclidine.

References and Notes

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

palladium on charcoal

palladium-on-carbon powder

alcohol,

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrogen chloride,
hydrochloric acid (7647-01-0)

ether (60-29-7)

hydrogen (1333-74-0)

chloroform (67-66-3)

magnesium (7439-95-4)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

iodine (7553-56-2)

acetone (67-64-1)

toluene (108-88-3)

isopropyl alcohol (67-63-0)

Ethyl chloroacetate (105-39-5)

potassium (7440-09-7)

Nicotinic acid (59-67-6)

potassium ethoxide (917-58-8)

Ethyl bromoacetate (105-36-2)

3-Quinuclidinone, hydrochloride,
3-Quinuclidone hydrochloride (1193-65-3)

ethyl isonicotinate (1570-45-2)

1-carbethoxymethyl-4-carbethoxypyridinium bromide

1-carbethoxymethyl-4-carbethoxypiperidine hydrobromide

1-carbethoxymethyl-4-carbethoxypiperidine (1838-39-7)

isonicotinic acid (55-22-1)

ethyl hexahydroisonicotinate (1126-09-6)

quinuclidine (100-76-5)

4-(2-hydroxyethyl)piperidine (622-26-4)

quinuclidone hydrochloride