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.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

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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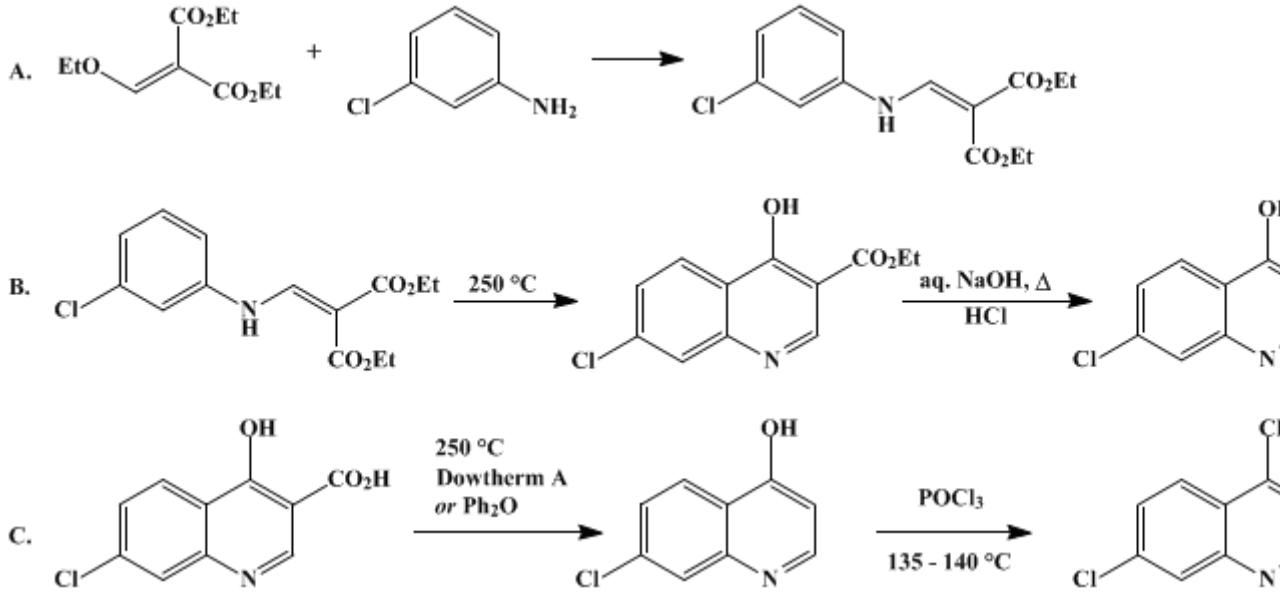
4,7-DICHLOROQUINOLINE

[Quinoline, 4,7-dichloro-]



Submitted by Charles C. Price and Royston M. Roberts[1].
Checked by J. R. Roland and R. S. Schreiber.

1. Procedure

A. *Ethyl α-carbethoxy-β-m-chloroanilinoacrylate*. A few boiling chips are added to a mixture of 127.5 g. (1.0 mole) of *m*-chloroaniline (Note 1) and 233 g. (1.1 moles) of ethyl ethoxymethylenemalonate (p. 395) (Note 2) in an open 500-ml. round-bottomed flask. The mixture is heated on a steam bath for 1 hour, the evolved ethanol being allowed to escape. The warm product is used directly in the next step (Note 3).

B. 7-*Chloro*-4-*hydroxy*-3-*quinolinecarboxylic acid*. In a 5-l. round-bottomed flask equipped with an air condenser 1 l. of Dowtherm A (Note 4) is heated to vigorous boiling, and the product of the above step is poured in through the condenser. Heating is continued for 1 hour, during which time a large proportion of the cyclization product crystallizes. The mixture is cooled, filtered, and washed with two 400-ml. portions of Skellysolve B (b.p. 61–70°) to remove the major portion of colored impurities. The air-dried filter cake (Note 5) is mixed with 1 l. of 10% aqueous sodium hydroxide, and the mixture is refluxed vigorously until all the solid ester dissolves (about 1 hour). The saponification mixture is cooled, and the aqueous solution is separated from any oil that may be present. The solution is acidified to Congo red paper with concentrated hydrochloric acid (ca. 270 ml. of the 38% acid, sp. gr. 1.19) or 10% sulfuric acid. The 7-chloro-4-hydroxy-3-quinolinecarboxylic acid, weight 190–220 g. (85–98%), is collected by filtration and washed thoroughly with water. The dry acid melts at about 266° with effervescence (Note 6).

C. 7-*Chloro*-4-*quinolinol and* 4,7-*dichloroquinoline*. The above air-dried acid (Note 7) is suspended in 1 l. of Dowtherm A in a 2-l. flask equipped with a stirrer and a reflux condenser. The mixture is boiled for 1 hour under a stream of nitrogen to assist in the removal of the water (Note 8). The clear, light-brown solution is cooled to room temperature, and 90 ml. (150 g., 0.98 mole) of phosphorus oxychloride is added. The temperature is raised to 135–140°, and the mixture is stirred for 1 hour. The reaction mixture is cooled and poured into a separatory funnel. The portion of the mixture adhering to the flask is rinsed into the funnel with ether, and the solution is washed with three 500-ml. portions of 10% hydrochloric acid. The combined acid extracts are cooled in ice and neutralized with 10% sodium

hydroxide to precipitate the 4,7-dichloroquinoline. The solid is collected, washed thoroughly with water, and dried; it weighs 130–145 g. (66–73%) and melts at 80–82°. The pure product is obtained by one recrystallization from Skellysolve B (b.p. 61–70°); weight 110–120 g. (55–60%), m.p. 84–85°.

2. Notes

1. The checkers found it desirable to distil the *m*-chloroaniline through a 20-plate column, the fraction boiling at 64–66°/18 mm. being collected for use in this preparation.
2. A good criterion of the purity of the ethyl ethoxymethylenemalonate is the refractive index; material of n_D^{25} > 1.4600 is satisfactory. The checkers redistilled the ethyl ethoxymethylenemalonate through a 1 by 12 in. bead-packed column just before use and employed the fraction boiling at 112–115°/0.1 mm., n_D^{25} 1.4604.
3. The anilinoacrylate can be recrystallized from low-boiling petroleum ether as slender white needles, m.p. 55–56°.
4. Dowtherm A, a mixture of biphenyl and diphenyl ether, may be replaced by diphenyl ether. The high-boiling solvent is most conveniently heated to its boiling point (ca. 250°) by an electric heating mantle.
5. The yield of ester isolated at this point is 215–240 g. (85–95%), m.p. 295–297°.
6. The acid can be recrystallized from ethanol as fine white needles melting with decomposition at 273–274°.
7. The acid need not be dry if care is taken to remove water during the decarboxylation in boiling Dowtherm.
8. If the 7-chloro-4-quinolinol is desired, it is more convenient to effect the decarboxylation without a solvent.[2]

3. Discussion

4,7-Dichloroquinoline has been prepared through a somewhat similar scheme from *m*-chloroaniline and oxaloacetic ester[3] or formylacetic ester.[4] The synthesis outlined above can be modified in various ways.[2,5,6,7]

The procedure has been utilized on a large scale in the preparation of several thousand pounds of 4,7-dichloroquinoline, essentially as described above. It has also been applied successfully to many other aromatic amines, including aniline,[8] *o*-,[9] and *m*-,[9] and *p*-anisidine,[3] 3,4-dimethylaniline,[3] *o*-nitroaniline,[8] *p*-chloroaniline,[8] *m*- and *p*-phenoxyaniline,[8] *p*-dimethylaminoaniline,[8] 3,4-dimethoxyaniline,[8] 3-aminopyridine,[3] *o*-phenylenediamine,[10] and 8-aminoquinoline.[10]

References and Notes

1. Work done under contract with the Office of Scientific Research and Development.
2. Price and Roberts, *J. Am. Chem. Soc.*, **68**, 1206 (1946).
3. Surrey and Hammer, *J. Am. Chem. Soc.*, **68**, 115 (1946).
4. Price, Leonard, and Reitsema, *J. Am. Chem. Soc.*, **68**, 1256 (1946).
5. Snyder and Jones, *J. Am. Chem. Soc.*, **68**, 1253 (1946).
6. Price and Roberts, *J. Am. Chem. Soc.*, **68**, 1255 (1946).
7. Price, Leonard, and Herbrandson, *J. Am. Chem. Soc.*, **68**, 1251 (1946); Price, Roberts, and Herbrandson, Brit. pat. 627,297 [*C. A.*, **44**, 2572 (1950)].
8. Riegel, Lappin, Adelson, Jackson, Albisetti, Dodson, and Baker, *J. Am. Chem. Soc.*, **68**, 1264 (1946).
9. Lauer, Arnold, Tiffany, and Tinker, *J. Am. Chem. Soc.*, **68**, 1268 (1946).
10. Snyder and Freier, *J. Am. Chem. Soc.*, **68**, 1320 (1946).

Appendix
Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

petroleum ether

Dowtherm A

Skellysolve B

formylacetic ester

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

Phosphorus Oxychloride (21295-50-1)

Biphenyl (92-52-4)

3,4-dimethoxyaniline (6315-89-5)

diphenyl ether (101-84-8)

3,4-Dimethylaniline (95-64-7)

4,7-Dichloroquinoline,
Quinoline, 4,7-dichloro- (86-98-6)

ethyl ethoxymethylenemalonate

7-Chloro-4-hydroxy-3-quinolinecarboxylic acid (86-47-5)

anilinoacrylate

7-chloro-4-quinolinol (86-99-7)

3-Aminopyridine (462-08-8)

8-aminoquinoline (578-66-5)

o-Phenylenediamine (95-54-5)

o-NITROANILINE (88-74-4)

m-chloroaniline (108-42-9)

p-chloroaniline (106-47-8)

p-anisidine (104-94-9)

p-dimethylaminoaniline (99-98-9)

Ethyl α-carbethoxy-β-m-chloroanilinoacrylate (3412-99-5)

p-phenoxyaniline (139-59-3)