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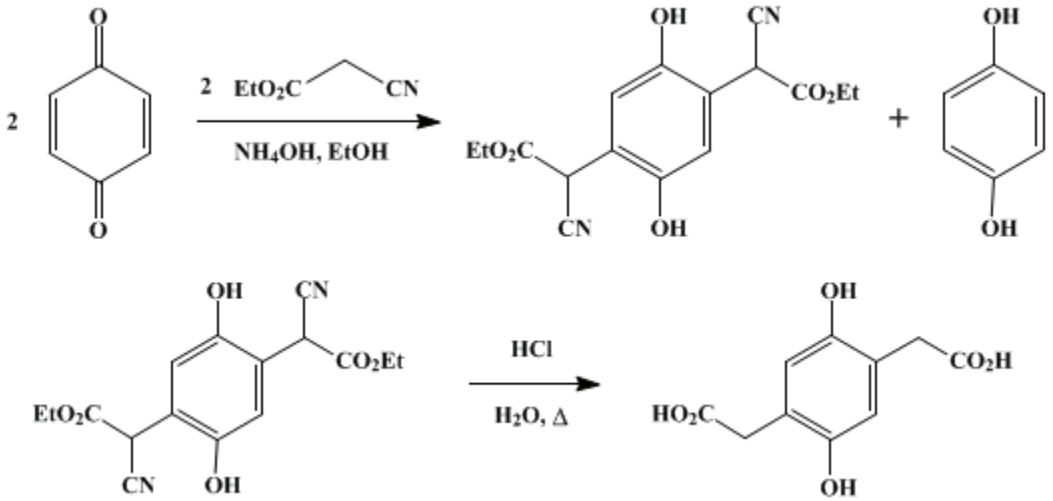
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.026.0024

Organic Syntheses, Coll. Vol. 3, p.286 (1955); Vol. 26, p.24 (1946).

2,5-DIHYDROXY-*p*-BENZENEDIACETIC ACID

[*p*-Benzenediacetic acid, 2,5-dihydroxy-]



Submitted by J. H. Wood and Lucile Cox.
Checked by Lee Irvin Smith, Scott Searles, and R. T. Arnold.

1. Procedure

A 3-l. round-bottomed three-necked flask is equipped with a mechanical stirrer, a 500-ml. dropping funnel, and a 250-ml. dropping funnel. The flask is contained in a pneumatic trough through which water at room temperature is circulated. A mixture of 30 ml. of ethyl cyanoacetate and 100 ml. of ethanol is placed in the flask. Meanwhile 54 g. (0.5 mole) of *p*-benzoquinone in a 1-l. flask is heated to 40° with 500 ml. of 95% ethanol, and, when practically all the quinone is dissolved, 56 g. (0.5 mole) of ethyl cyanoacetate is added and the mixture is stirred until solution is complete (Note 1). Most of this solution is placed in the 500-ml. dropping funnel, the remainder being added when the funnel becomes sufficiently emptied after the reaction has started.

Twenty-five milliliters of concentrated ammonium hydroxide (Note 2) is introduced into the 3-l. flask. A solution of 100 ml. of concentrated ammonium hydroxide in 150 ml. of water is placed in the 250-ml. dropping funnel, which is loosely stoppered. Stirring is started, and the stopcocks of the two dropping funnels are adjusted so that the solutions will be delivered into the flask at a uniform rate in a period of about 45 minutes (Note 3). Stirring is continued for an additional 10 minutes. The mixture is then permitted to stand for 1 hour, after which the purplish red precipitate is filtered with suction. Any solid material adhering to the walls of the flask is washed onto the funnel with ethanol. The solid is then washed three times on the funnel with ethanol (Note 4). The filtrate and washings are discarded. The product is slightly impure diethyl α,α'-dicyano-2,5-dihydroxy-*p*-benzenediacetate and weighs 36–41 g. (43–49%) (Note 5).

For the hydrolysis, 36 g. (0.11 mole) of the residue is transferred to a 1-l. round-bottomed flask equipped with a reflux condenser, and 210 ml. of concentrated hydrochloric acid in 190 ml. of water is added. The mixture is refluxed gently at first, then vigorously (Note 6), until hydrolysis is essentially complete (about 20 hours). Then 180 ml. of water and 4 g. of Norit A are added and the mixture is stirred and boiled for 3 minutes, after which it is rapidly filtered with suction through two layers of hardened filter paper in a Büchner funnel (Note 7). The filtrate, upon cooling to 20° or below, deposits 18 g. (72%) of lightly colored 2,5-dihydroxy-*p*-benzenediacetic acid (Note 8). A snow-white product is obtained by dissolving 18 g. of this material in 375 ml. of boiling water, treating with 2 g. of Norit A, and filtering. Upon cooling, there is deposited 15 g. (61%) of the acid which melts at 233° (Note 9).

2. Notes

1. Precautions must be taken to prevent ammonia from coming in contact with the quinone before the desired time. The dropping funnel is loosely stoppered, and the flask containing the remainder of the solution is well stoppered.
2. Concentrated ammonium hydroxide (28% NH_3) must be used to obtain a good yield. The ammonium hydroxide may be introduced through either the central opening or the 250-ml. dropping funnel with the precaution given in (Note 1).
3. Preferably, all the ammonium hydroxide solution should be added by the time 90% of the quinone solution has been added.
4. This product is insoluble in ethanol, and there is no loss in washing.
5. Slightly lower yields were obtained by the checkers at this point. The yields in three experiments were respectively 32.5, 32.0, and 31.5 g. (39, 38.5, and 38%).
6. In the early stages, considerable foaming usually occurs, and care must be exercised that the foam does not carry part of the insoluble product into the condenser. The insoluble material accumulating on the walls of the flask is occasionally returned to the liquid portion by whirling the flask.
7. Rapid filtration is essential to avoid crystallization in the funnel and to decrease the time the filter paper is in contact with the concentrated acid.
8. The checkers obtained, in two experiments, yields of 71 and 86% of material melting respectively at 232–238° (cor.) and 235–239° (cor.).
9. The checkers obtained, in two experiments, yields of 63 and 73% at this point. The product was white and melted at 233° (cor.).

3. Discussion

The method described above is a modification of that described by Wood, Colburn, Cox, and Garland.[1]

References and Notes

1. Wood, Colburn, Cox, and Garland, *J. Am. Chem. Soc.*, **66**, 1540 (1944).

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

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Norit A (7782-42-5)

ammonium hydroxide (1336-21-6)

Ethyl cyanoacetate (105-56-6)

Quinone,
p-benzoquinone (106-51-4)

2,5-Dihydroxy-p-benzenediacetic acid,
p-Benzenediacetic acid, 2,5-dihydroxy- (5488-16-4)

diethyl α,α'-dicyano-2,5-dihydroxy-p-benzenediacetate