



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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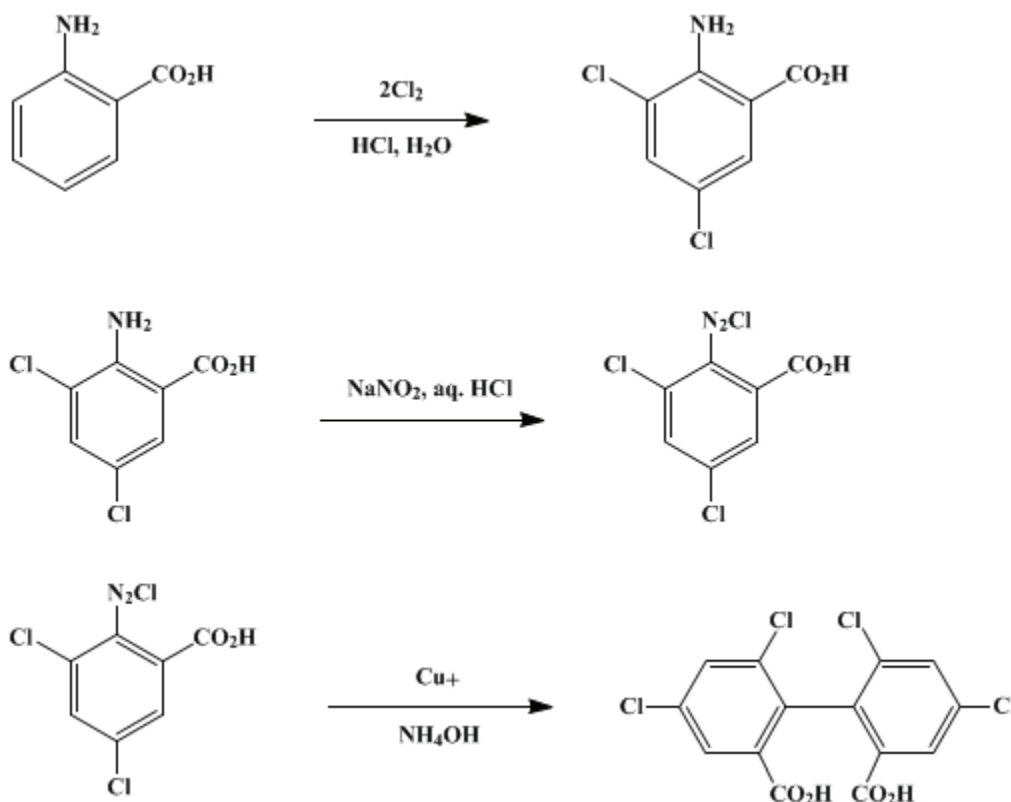
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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***dl*-4,4',6,6'-TETRACHLORODIPHENIC ACID**

[*dl*-Diphenic acid, 4,4',6,6'-tetrachloro-]



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1. Procedure

A. *3,5-Dichloro-2-aminobenzoic acid*. A solution of 45 g. (0.33 mole) of *anthranilic acid*, 150 ml. of concentrated *hydrochloric acid*, and 850 ml. of water is placed in a 2-l. three-necked flask in a hood and weighed. While the solution is stirred rapidly, *chlorine* is introduced until the reaction mixture gains 45 g. (0.63 mole) in weight (Note 1). The flask is surrounded by a water bath to maintain the temperature of the reaction mixture below 30° during the chlorination procedure. The reaction mixture is filtered by suction, using a large (10–12 in.) Büchner funnel; the crude product is washed with water and then dried at room temperature (Note 2). There is obtained 55–65 g. of crude product melting at about 205° . The crude product is leached with 4 ml. of boiling *benzene* per gram, filtered by suction, and washed on the filter with 1 ml. of cold *benzene* per gram. After drying at room temperature, there is obtained 46.5–53 g. (69–78%) of crude *3,5-dichloro-2-aminobenzoic acid*. The melting point of this material should not be lower than 211° (Note 3) and (Note 4).

B. *Diazotization of 3,5-dichloro-2-aminobenzoic acid*. Fifty grams (0.24 mole) of *3,5-dichloro-2-aminobenzoic acid* is dissolved in a solution of 12 g. (0.3 mole) of *sodium hydroxide* in 700 ml. of water. To this solution is added 20 g. (0.29 mole) of *sodium nitrite*, and the solution is cooled to 10° (Note 5). One hundred milliliters of concentrated *hydrochloric acid* (sp. gr. 1.191) and 200 ml. of water are placed in a 2-l three-necked flask and cooled to 10° . The cold solution of *sodium 3,5-dichloro-2-aminobenzoate* and *sodium nitrite* is then added to the *hydrochloric acid* solution with cooling (10°) and efficient stirring at such a rate that no appreciable accumulation of undiazotized amine results (Note 6). At the conclusion of the diazotization, the resulting solution is stirred a few minutes with 2 g. of

diatomaceous earth and filtered by suction (Note 7).

C. *Preparation of the reducing agent.* One hundred and twenty-five grams (0.5 mole) of cupric sulfate pentahydrate is dissolved in 500 ml. of water contained in a 3-l. three-necked flask equipped with a mechanical stirrer, and then 210 ml. of concentrated ammonium hydroxide (sp. gr. 0.90) is added with stirring. The solution is cooled to 10°. A solution of 40 g. (0.57 mole) of hydroxylamine hydrochloride in 140 ml. of water is prepared and also cooled to 10°. To the hydroxylamine hydrochloride solution there is added 95 ml. of 6*N* sodium hydroxide solution, and if not entirely clear, it is filtered by suction. This hydroxylamine solution is immediately added to the ammoniacal cupric sulfate solution with stirring. Reduction occurs at once with the evolution of nitrogen, and the solution becomes pale blue. If this solution is not used at once, it should be protected from the air.

D. *dl-4,4',6,6'-Tetrachlorodiphenic acid.* The reducing solution prepared above is cooled to 10° and maintained at 10–15° during the addition of the diazo solution from Part B, which is added from dropping funnel. A feed tube having a 2-mm. opening and dipping well below the surface of the reducing solution should be attached to the stem of the dropping funnel. The feed tube should be bent upward at the end and so placed that mixing of the reducing solution occurs rapidly (Note 8). The diazo solution is added at approximately 25 ml. per minute, and excessive foaming is suppressed by the addition of small amounts of ether (Note 9). At the conclusion of the reaction (Note 10), the ammoniacal solution is transferred to two 4-l. beakers, heated to 80–90°, and rapidly acidified to litmus with concentrated hydrochloric acid with vigorous stirring (Note 11). At this point acidification is continued more carefully until the solution is acid to Congo red (Note 12). A total excess of 100 ml. of acid is then added, and the solution is allowed to stand overnight. The product is filtered by suction and washed on the filter with four 250-ml. portions of water. After drying, the yield of crude product, melting at 180–215°, is 29–38.5 g. (63–84%).

The crude product is dissolved in 3.5 ml. of concentrated sulfuric acid per gram, heated with stirring to 150° for 5 minutes, and allowed to cool overnight. The resulting product is filtered by suction through a sintered-glass funnel and washed on the filter with three 15-ml. portions of concentrated sulfuric acid at room temperature. The filter cake is removed from the funnel and boiled with 50 ml. of water to remove adherent sulfuric acid. The product is then filtered and dried. The above procedure yields 19–22 g. (41–48%) of almost colorless *dl-4,4',6,6'-tetrachlorodiphenic acid* melting at 243–250° (uncor.) (Note 13). Pure acid may be obtained by a second recrystallization from concentrated sulfuric acid. Twenty grams of crude *dl-4,4',6,6'-tetrachlorodiphenic acid*, m.p. 243°, recrystallized from 70 ml. of concentrated sulfuric acid yields 6.54 g. (33% recovery) of colorless product melting at 258–259°.

2. Notes

1. The rate of flow of chlorine is adjusted so that the reaction mixture is saturated with gas and some gas escapes from the surface of the solution. An indication of proper duration of chlorination is the development of a distinct brown color in the suspension. Further chlorination leads to a decrease in yield with the formation of polychloro products.² The time required for chlorination is about 1 hour.
2. Drying at elevated temperatures gives an inferior product because of the formation of polychloro by-products at this stage.
3. Pure 3,5-dichloro-2-aminobenzoic acid³ has a melting point of 231°. The product described here is adequate for the subsequent step.
4. This procedure can be performed using 10 times the quantities specified. The chlorination is carried out in a jar having a capacity of 12–14 l. Chlorine is introduced by means of a copper tube coiled at the bottom of the jar and perforated in several places. The time of chlorination is 2 hours. The percentage yield is the same as that for the scale described above.
5. This solution is almost saturated with the sodium salt of 3,5-dichloro-2-aminobenzoic acid. If crystallization occurs, additional water may be added. Obviously, temperatures below 10° should be avoided.
6. As the salt solution enters the acid solution, there is a momentary precipitation of the amino acid, which dissolves rapidly as it is diazotized. The checkers found that this addition took about 2 hours.
7. The diazo solution may be stored as long as 1 day at 10–15°. The insoluble gelatinous material that forms during storage should be removed by filtration just before use. The filter flask used at this point

should be cooled in an ice bath to prevent further decomposition of diazo solution.

8. This trap arrangement prevents premature reaction of the entering diazo solution with ammonia, which otherwise would be carried up the feed tube by ascending bubbles of nitrogen.

9. The rate of addition is not a critical factor. More rapid addition requires more vigorous stirring and may lead to troublesome foaming.

10. The solution may stand for a week before being used.

11. The checkers recommend the use of a Hershberg stirrer.

12. Basic copper salts which precipitate during the acidification redissolve before the Congo red end point is reached if the later stages of acidification are performed carefully with adequate stirring.

13. This procedure is adaptable to 10 times the quantities specified here. Diazotization is carried out in a 12-l. jar. The diazo solution is allowed to stand overnight to facilitate the separation, by decantation or siphoning, of the non-diazotizable impurities whose large-scale filtration is tedious. The main synthesis is performed in a carboy having a capacity of not less than 30 l. The metal stirrer is protected by a coat of paraffin wax. Several addition tubes are used for the diazo solution. By adding appropriate quantities of ice, the necessity of external cooling for these large vessels is avoided. The yield is 39–42% of material melting at 244–250°.

3. Discussion

3,5-Dichloro-2-aminobenzoic acid can be prepared by the chlorination of anthranilic acid in glacial acetic acid solution³ and by the action of sulfuryl chloride on anthranilic acid.^{4,5} The procedure above is derived from a detailed study of the chlorination reaction.²

The method described for the preparation of *dl*-4,4',6,6'-tetrachlorodiphenic acid is based on the work of Atkinson and Lawler⁶ but employs a more suitable reducing agent than that⁷ previously used to convert diazotized anthranilic acid to diphenic acid. The product can be resolved into its optically active forms,⁶ which are stable to racemization.

References and Notes

1. University of New Hampshire, Durham, New Hampshire.
 2. Atkinson and Mitton, *J. Am. Chem. Soc.*, **69**, 3142 (1947).
 3. Elion, *Rec. trav. chim.*, **44**, 1106 (1925).
 4. Eller and Klemm, *Ber.*, **55**, 222 (1922).
 5. Durrans, *J. Chem. Soc.*, **123**, 1424 (1923).
 6. Atkinson and Lawler, *J. Am. Chem. Soc.*, **62**, 1704 (1940).
 7. *Org. Syntheses Coll. Vol. 1*, 222 (1941).
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Appendix

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

dl-4,4',6,6'-TETRACHLORODIPHENIC ACID

dl-Diphenic acid, 4,4',6,6'-tetrachloro-

dl-4,4',6,6'-tetrachlorodiphenic acid

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

[acetic acid \(64-19-7\)](#)

[ammonia \(7664-41-7\)](#)

[Benzene \(71-43-2\)](#)

[ether \(60-29-7\)](#)

[sodium hydroxide \(1310-73-2\)](#)

[nitrogen \(7727-37-9\)](#)

[cupric sulfate \(7758-98-7\)](#)

[sodium nitrite \(7632-00-0\)](#)

[copper \(7440-50-8\)](#)

[sulfuryl chloride \(7791-25-5\)](#)

[chlorine \(7782-50-5\)](#)

[ammonium hydroxide \(1336-21-6\)](#)

[Anthranilic Acid \(118-92-3\)](#)

[Hydroxylamine hydrochloride \(5470-11-1\)](#)

[cupric sulfate pentahydrate \(7758-99-8\)](#)

[3,5-Dichloro-2-aminobenzoic acid \(2789-92-6\)](#)

[sodium 3,5-dichloro-2-aminobenzoate,
sodium salt of 3,5-dichloro-2-aminobenzoic acid](#)