



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.

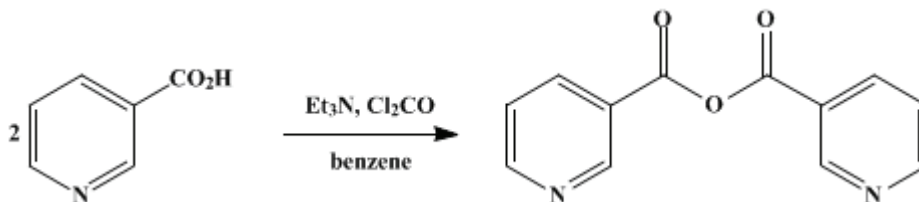
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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NICOTINIC ANHYDRIDE



Submitted by Heinrich Rinderknecht and Morris Gutenstein¹.

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1. Procedure

Nicotinic acid (10 g., 0.081 mole) (Note 1) and anhydrous benzene (275 ml.) (Note 2) are placed in a 500-ml. three-necked, round-bottomed flask (Note 3) fitted with a sealed Hershberg stirrer, a dropping funnel with a pressure-equalizing tube, and a stillhead connected to a condenser. In order to remove traces of moisture introduced with the nicotinic acid the mixture is heated until about 75 ml. of benzene has distilled. The stillhead is replaced by a Claisen head fitted with a thermometer and a calcium chloride tube, and the mixture is cooled to 5° by stirring in an ice bath. To the cold suspension of nicotinic acid is added all at once 8.65 g. (0.086 mole, 5% excess) of triethylamine (Note 4). The resulting clear solution is stirred with continued cooling while 34 g. of a 12.5% solution of phosgene (0.043 mole, 5% excess) in benzene (Note 5) is added through the dropping funnel. The rate of addition is regulated so that the temperature of the reaction mixture does not exceed 7°. Triethylamine hydrochloride precipitates immediately. After the addition of phosgene the mixture is stirred at room temperature for 45 minutes, heated to the boiling point, and filtered under slightly reduced pressure (Note 6) while hot. The triethylamine hydrochloride cake (Note 7) is washed on the filter with three 25-ml. portions of warm benzene (60°). The combined filtrate and washes are transferred to a 500-ml. round-bottomed flask and evaporated to dryness on a rotary evaporator at low temperature and pressure. The dry residue is simmered with 75 ml. of anhydrous benzene (Note 2), and the mixture is filtered while hot. The triethylamine hydrochloride cake (Note 7) is washed with two 5-ml. portions of cold benzene, and the filtrate and washes are allowed to stand at 20° for 2–3 hours. The crystalline product is collected on a filter, washed with two 4-ml. portions of cold anhydrous benzene, and dried in a vacuum. The yield of nicotinic anhydride, m.p. 122–125° (Note 8), is 6.25 g. (68%). The combined filtrate and washes are evaporated to dryness on a rotary evaporator. The residue is simmered with 175 ml. of a mixture of benzene and cyclohexane (2:3) (Note 2), and a small amount of insoluble material is removed by filtration of the hot mixture (Note 6). The filtrate is stored at 5° for 18 hours (Note 9); the crystalline deposit is collected, washed with 3 ml. of cold benzene-cyclohexane mixture, and dried in a vacuum. An additional 2.4 g. (25%) of colorless product, m.p. 122–123°, is thus obtained. The total yield of nicotinic anhydride is 8.05–8.65 g. (87–93%).

2. Notes

1. Nicotinic acid supplied by Matheson, Coleman and Bell yielded a colorless anhydride; U.S.P. grade material gave a slightly buff-colored product.
2. Benzene and cyclohexane are freshly distilled and stored over sodium wire or calcium hydride.
3. Nicotinic anhydride is extremely sensitive to moisture; all glassware is therefore dried overnight in an oven at 200° before use.
4. Triethylamine is freshly distilled and stored over potassium hydroxide pellets.
5. A 12.5% solution of phosgene in benzene is available from Matheson, Coleman and Bell.
6. It is essential to carry out filtration under only slightly reduced pressure in order to minimize evaporation, cooling, and crystallization in the filter plate and funnel.
7. The yield of triethylamine hydrochloride obtained in this and subsequent extractions amounts to over 96% of that expected.

8. Melting points were determined in capillary tubes and are corrected. Reported:² 123–126°.
9. Rigorously anhydrous conditions are essential throughout this procedure and the flask must be air-tight.

3. Discussion

The present method is that described by Rinderknecht and Ma.³ It is equally applicable to a variety of other heterocyclic, aromatic, and aliphatic anhydrides.^{4,5} Nicotinic anhydride was first prepared by reaction of nicotinoyl chloride with sodium nicotinate,^{6,7} and more recently by reaction of potassium nicotinate with oxalyl chloride in anhydrous benzene.²

4. Merits of the Preparation

The present method of preparing anhydrides is distinguished from other procedures by its simplicity and high yield. It avoids the two-phase reaction systems of older methods and the need for often inaccessible and highly sensitive acid chlorides. The only nongaseous by-product, triethylamine hydrochloride, is readily removed from the reaction mixture and leaves, in nearly quantitative yield, a solution of product suitable for further reaction or isolation.

References and Notes

1. Contribution No. 3176 from the Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California. This work was supported by grant No. HD-00347 from the National Institute of Child Health and Human Development.
 2. A. W. Schrecker and P. B. Maury, *J. Am. Chem. Soc.*, **76**, 5803 (1954).
 3. H. Rinderknecht and V. Ma, *Helv. Chim. Acta*, **47**, 162 (1964).
 4. T. Wieland and H. Bernhard, *Ann.*, **572**, 190 (1951).
 5. T. K. Brotherton, J. Smith, Jr., and J. W. Lynn, *J. Org. Chem.*, **26**, 1283 (1961).
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Appendix

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

benzene-cyclohexane

Benzene (71-43-2)

cyclohexane (110-82-7)

potassium hydroxide (1310-58-3)

phosgene (75-44-5)

Triethylamine hydrochloride (554-68-7)

Nicotinic acid (59-67-6)

oxalyl chloride (79-37-8)

triethylamine (121-44-8)

Nicotinic anhydride (16837-38-0)

nicotinoyl chloride

sodium nicotinate (54-86-4)

potassium nicotinate (16518-17-5)