



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.

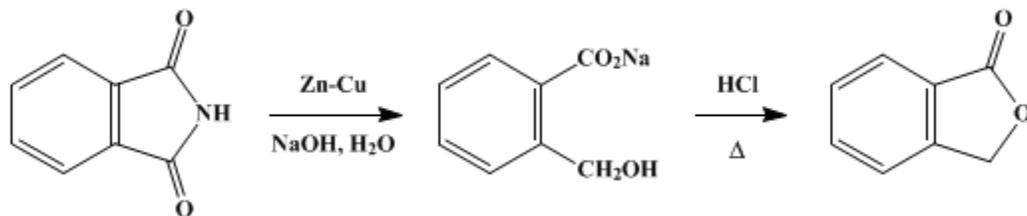
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior 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.

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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.

Organic Syntheses, Coll. Vol. 2, p.526 (1943); Vol. 16, p.71 (1936).

PHTHALIDE



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1. Procedure

In a 2-l. round-bottomed flask, 180 g. (2.75 gram atoms) of **zinc** dust is stirred to a thick paste with a solution of 1 g. of **copper sulfate** in about 35 cc. of water (**Note 1**), and 400 g. (327 cc.) of 20 per cent aqueous **sodium hydroxide** is added. The flask is equipped with a mechanical stirrer, the contents are cooled to 5° by means of an ice bath, and 147 g. (1 mole) of **phthalimide** (*Org. Syn. Coll. Vol. I, 1941, 457*) is added in small portions at such a rate that the temperature does not rise above 8° (about thirty minutes is required). After all the **phthalimide** has been added, stirring is continued for one-half hour. The mixture is diluted with 400 cc. of water, warmed on a steam bath until evolution of **ammonia** has ceased (about three hours), and concentrated to a volume of about 400 cc. by distillation under reduced pressure. The material is filtered and the filtrate made acid to Congo red with concentrated **hydrochloric acid** (about 150 cc. is required). The mixture, in which the **phthalide** has separated as an oil, is boiled for one hour in order to complete the lactonization of the **hydroxymethylbenzoic acid**, and transferred while hot to a beaker. On cooling, the oily product solidifies to a hard red-brown cake. After chilling overnight in a refrigerator, when a further quantity of crystalline solid separates from the aqueous layer, the cold mixture is filtered with suction (**Note 2**). The crude **phthalide**, which contains a considerable quantity of **sodium chloride**, is recrystallized in 20-g. portions from 1.5 l. of water; the mother liquor from the first crop is employed for recrystallization of the subsequent portions. Each portion is filtered hot and cooled below 5° before collecting the crystals, which are finally washed with small quantities of ice-cold water (**Note 3**). The **phthalide** crystallizes in transparent plates which melt at 72–73°. The yield is 90–95 g. (67–71 per cent of the theoretical amount) (**Note 4**).

2. Notes

1. In checking these directions complete failure was repeatedly encountered with good commercial grades of **zinc** dust, and only when the metal was activated with **copper sulfate** did reduction proceed at all.
2. The mother liquor, on concentrating to less than half its volume, yields no further crystals on chilling.
3. On cooling, a minute amount of a yellow impurity separates with the **phthalide** at the beginning of crystallization. This impurity apparently cannot be eliminated by boiling with charcoal but is present in too small amount to affect the melting point of the product.
4. Concentration of the final mother liquor to a volume of 500 cc. yields a further small quantity of **phthalide**, but this operation is scarcely worth while.

3. Discussion

Phthalide has been prepared by the bromination of *o*-**toluic acid** followed by hydrolysis;¹ by the reduction of **phthalic anhydride**,² **ammonium phthalate**,³ or ethyl acid phthalate;⁴ and by the method described in the procedure above.⁵

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 174
- Org. Syn. Coll. Vol. 3, 737
- Org. Syn. Coll. Vol. 4, 810
- Org. Syn. Coll. Vol. 5, 145

References and Notes

1. Hjelt, Ber. **19**, 412 (1886); Salkind and Ssemenow, J. Russ. Phys.-Chem. Soc. **46**, 512 (1914) (Chem. Zentr. **1914**, II, 1271); Davies and Perkin, J. Chem. Soc. **121**, 2207 (1922).
 2. Wislicenus, Ber. **17**, 2181 (1884); Godchot, Bull. soc. chim. (4) **1**, 830 (1907); Sabatier and Kubota, Compt. rend. **172**, 736 (1921); Austin, Bosquet, and Lazier, J. Am. Chem. Soc. **59**, 864 (1937).
 3. Delfino and Somlo, IX Congr. intern. quím. pura applicada **4**, 360 (1934) [C. A. **30**, 2855 (1936)].
 4. E. I. du Pont de Nemours and Company, U. S. pat. 2,114,696 [C. A. **32**, 4607 (1938)].
 5. Reissert, Ber. **46**, 1489 (1913); Kalle and Company, A.-G., Ger. pat. 267,596 [Frld. **11**, 196 (1912-14)].
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Appendix Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Congo red

ethyl acid phthalate

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

copper sulfate (7758-98-7)

phthalic anhydride (85-44-9)

zinc (7440-66-6)

Phthalimide (85-41-6)

ammonium phthalate (523-24-0)

Phthalide (87-41-2)

hydroxymethylbenzoic acid (612-20-4)

o-Toluic acid (118-90-1)

