



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.

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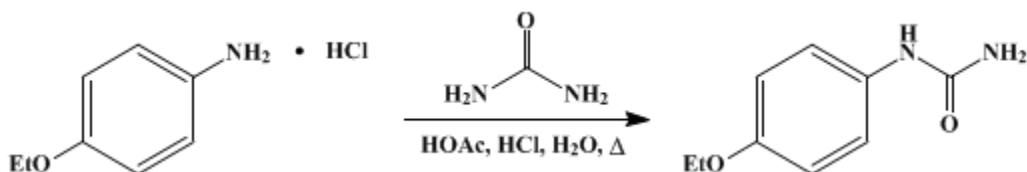
ARYLUREAS

II. UREA METHOD

p-ETHOXYPHENYLUREA

[Dulcin]

[Urea, *p*-ethoxyphenyl-]



1. Procedure

A mixture of 870 g. (5 moles) of *p*-phenetidine hydrochloride and 1.2 kg. (20 moles) of urea is placed in a 12-l. round-bottomed flask (Note 1). To this mixture are added 2 l. of water, 40 ml. of concentrated hydrochloric acid, and 40 ml. of glacial acetic acid, and the well-shaken suspension is heated to boiling. The dark purple solution thus obtained is boiled vigorously for 45–90 minutes until the reaction is complete. The liquid remains clear during the first half of the heating period. Separation of the product begins during the last half and proceeds with increasing rapidity until the entire contents of the vessel suddenly set to a solid mass. The source of heat is immediately withdrawn at this point (Note 2).

After cooling to room temperature, the product is broken up with the addition of 1–1.5 l. of water, filtered with suction, washed with cold water, drained, and dried. The crude *p*-ethoxyphenylurea is obtained in a yield of 740–810 g. (82–90%) as a nearly white to pale yellow solid (Note 3). This material may be purified by recrystallization from boiling water (Note 4), when minute white plates, m.p. 173–174°, are obtained. The method is applicable to the preparation of other substituted arylureas (Note 5).

2. Notes

1. An enameled-steel vessel of approximately 2-gal. capacity is suitable for carrying out this reaction.
2. After removal of the heat source, a vigorous reaction may continue for a few minutes, and the reaction mixture tends to froth somewhat. It eventually sets to a sponge-like formation of a crystalline mass. In smaller-scale experiments the final stage of the reaction is more easily controlled. The checkers employed one-tenth the scale and conventional equipment.
3. The crude product contains varying small quantities of the symmetrical disubstituted compound, di-(*p*-ethoxyphenyl)urea [$(p\text{-C}_2\text{H}_5\text{OC}_6\text{H}_4\text{NH})_2\text{CO}$]. This substance is removed in the crystallization from water (Note 4).
4. To 1 l. of boiling water, 35 g. of crude *p*-ethoxyphenylurea is added. The bulk of the urea dissolves readily, and the solution is decolorized by the addition of 3 g. of activated charcoal, boiled for 5 minutes, and quickly filtered with suction through a pre-heated Büchner funnel. The colorless filtrate is slowly cooled to 0°, when lustrous minute plates of *p*-ethoxyphenylurea separate. An 80% recovery of material having m.p. 173–174° is obtained. Prolonged boiling of the solution should be avoided, since slow conversion to *sym*-di-(*p*-ethoxyphenyl) urea occurs under these conditions.
5. *p*-Anisidine hydrochloride (0.5 mole), When boiled with the proportionate quantities of urea and other reagents for 1 hour, gives 80–85% yields of *p*-methoxyphenylurea. Owing to the greater solubility of this product in water, less of the material separates during the heating period, but satisfactory crystallization occurs when the reaction liquid is slowly cooled to 0°. 1-Amino-2-naphthol hydrochloride gives 72–87% yields of 1-(2-hydroxy-1-naphthyl)urea.

3. Discussion

p-Ethoxyphenylurea has been prepared by the action of potassium cyanate on *p*-phenetidine hydrochloride¹ or *p*-phenetidine acetate,² and by the interaction of *p*-phenetidine with the following agents: phosgene in benzene or toluene and treatment of the product with ammonia;³ urethan;⁴ urea salts;⁵ acetylurea;⁶ and a mixture of urea and ammonium chloride.⁷ It has been obtained from the reaction of phenetidine salts (usually the hydrochloride) with urea,^{5,8} or with a mixture of sodium cyanide and sodium hypochlorite or peroxide.⁹ *p*-Ethoxyphenylurea has also been prepared by heating *p*-ethoxyphenylurethan and ammonia to 100–180°;⁴ by heating di-(*p*-ethoxyphenyl)urea with urea, ammonium carbamate, commercial ammonium carbonate,¹⁰ or ethanol and ammonia;¹¹ by treating ammonium *p*-ethoxyphenyldithiocarbamate with lead carbonate in alcoholic solution;¹² by ethylating *p*-hydroxyphenylurea;¹³ and by the action of ammonia on *p*-ethoxyphenyl isocyanate.¹⁴

References and Notes

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Appendix

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

Dulcin

sym-di-(*p*-ethoxyphenyl) urea

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonium carbonate (506-87-6)

ammonia (7664-41-7)

Benzene (71-43-2)

ammonium chloride (12125-02-9)

sodium cyanide (143-33-9)

toluene (108-88-3)

phosgene (75-44-5)

urea (57-13-6)

ammonium carbamate (1111-78-0)

peroxide (7722-84-1)

sodium hypochlorite (7681-52-9)

potassium cyanate (590-28-3)

1-amino-2-naphthol hydrochloride (1198-27-2)

urethan (51-79-6)

1-(2-hydroxy-1-naphthyl)urea

acetylurea (591-07-1)

p-phenetidine (156-43-4)

p-phenetidine hydrochloride (637-56-9)

p-Methoxyphenylurea (1566-42-3)

p-Ethoxyphenylurea,
Urea, p-ethoxyphenyl- (150-69-6)

di-(p-ethoxyphenyl)urea

p-Anisidine hydrochloride (20265-97-8)

p-phenetidine acetate

p-ethoxyphenylurethan

ammonium p-ethoxyphenyldithiocarbamate

p-hydroxyphenylurea

p-ethoxyphenyl isocyanate (32459-62-4)

lead carbonate

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