



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](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.

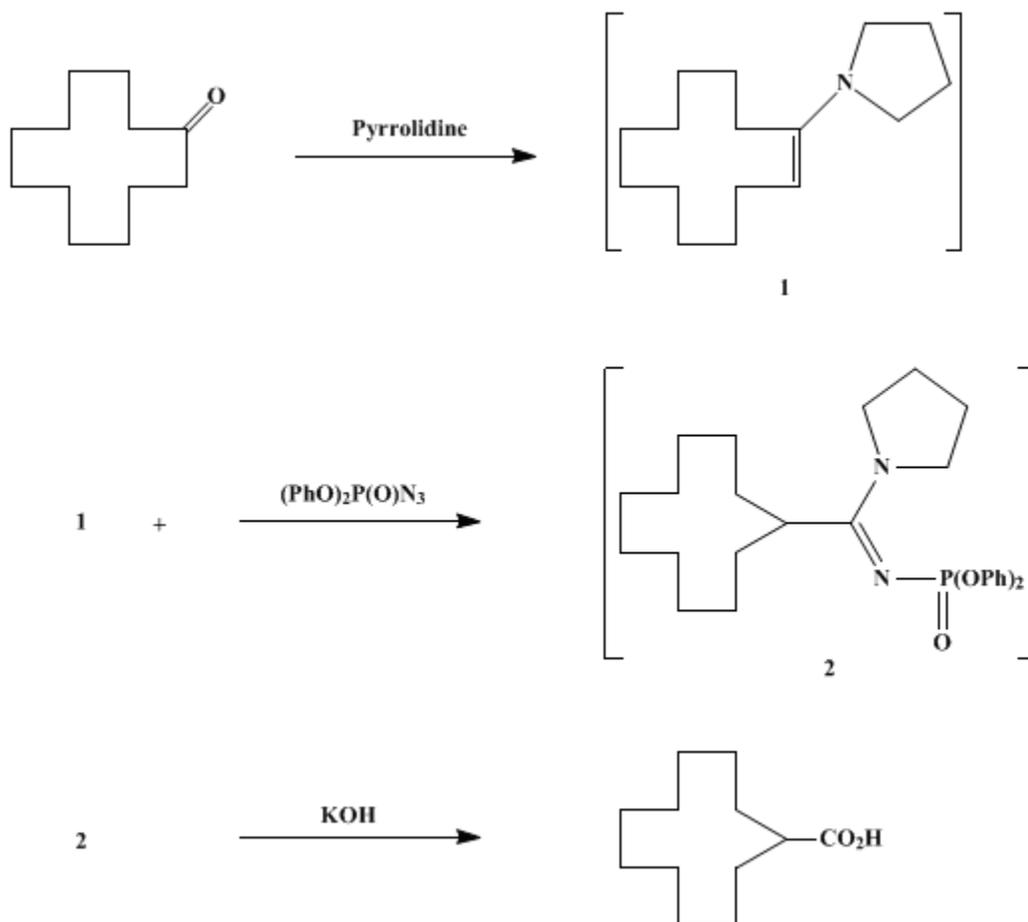
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior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

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

*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. 7, p.135 (1990); Vol. 62, p.191 (1984).*

## CYCLOUNDECANECARBOXYLIC ACID



Submitted by Yasumasa Hamada and Takayuki Shioiri<sup>1</sup>.  
Checked by M. F. Semmelhack and E. Spiess.

### 1. Procedure

To a 300-mL, round-bottomed flask fitted with a water separator (Note 1) that contains 15 g of Linde 4A molecular sieve 1/16-in. pellets and is filled with toluene, are added 7.3 g (0.04 mol) of cyclododecanone, 11.4 g (0.16 mol) of pyrrolidine, 100 mL of toluene, and 0.57 g (0.004 mol) of boron trifluoride etherate. The solution is heated under reflux for 20 hr. The water separator is replaced by a distillation head, and about 90 mL of the toluene is removed by distillation at atmospheric pressure. The residue containing 1-(N-pyrrolidino)-1-cyclododecene (**1**) is used in the next step without further purification (Note 2).

The crude enamine (**1**) is dissolved in 20 mL of toluene, and the solution is transferred (Note 3) to a 100-mL, three-necked flask equipped with a magnetic stirring bar, a 50-mL dropping funnel, reflux condenser protected with a calcium chloride tube, and a thermometer immersed in the solution. A solution of 13.2 g (0.048 mol) of diphenyl phosphorazidate (Note 4); *Warning* in 20 mL of toluene is added with stirring during 30 min while the reaction temperature is maintained at about 25°C. The mixture is stirred for 4 hr at 25°C and heated at reflux for 1 hr. The mixture is transferred to a 300-mL, round-bottomed flask and most of the toluene is removed under reduced pressure to yield 23.7 g of a reddish-brown oil, **2** (Note 5).

Ethylene glycol (200 mL) and 40 g (0.71 mol) of potassium hydroxide are added to the residual oil.

The mixture is heated at reflux for 24 hr and then concentrated at 80–115°C (25 mm) (bath temperature ca. 190°C) until 100 mL of distillate is collected. The residue is dissolved in 300 mL of water and cooled to room temperature. Carbon dioxide is introduced as a gas until the pH of the solution reaches 9. The mixture is washed with three 80-mL portions of diethyl ether (Note 6). The aqueous layer is acidified with about 53 mL of concentrated hydrochloric acid and extracted with four 80-mL portions of benzene. The combined benzene extracts are washed with 50 mL of water and dried over anhydrous sodium sulfate. The solvent is removed under reduced pressure to give 4.5–5.5 g of a black-brown oil. Distillation of the oil at 110–115°C (0.1 mm) yields 3.5–3.8 g (40–48%) of cycloundecanecarboxylic acid as a colorless oil.

## 2. Notes

1. The apparatus described in *Organic Syntheses*<sup>2</sup> is satisfactory.
2. Pure 1-(*N*-pyrrolidino)-1-cyclododecene, bp 144°C (1.5 mm), may be isolated by distillation through a Vigreux column.
3. The original flask used for the enamine formation can be used after the attachment of a Y-shaped tube fitted with a dropping funnel and a reflux condenser protected with a tube packed with a drying agent such as anhydrous calcium chloride.
4. Diphenyl phosphorazidate is prepared by the action of sodium azide with diphenyl phosphorochloridate<sup>3</sup>. It is also available from Aldrich Chemical Co. and was used after purification by distillation at 134–136°C (0.2 mm). *Warning: Diphenyl phosphorazidate may produce explosive hydrogen azide when it is in contact with moisture for a long time. When diphenyl phosphorazidate, which has been stored for a long time, is used, it should be washed with saturated aqueous sodium bicarbonate and dried over sodium sulfate before distillation.*
5. Purification of 1 g of the crude oil was made by column chromatography using 50 g of Merck silica gel with 0.063–0.200-mm particles (catalog No. 7734) in a column 2.2-cm × 40-cm and 1:1 (v/v) ethyl acetate-hexane as eluant to give pure diphenyl (cycloundecyl-1-pyrrolidinylmethylene)phosphoramidate (2) as a colorless oil, 632 mg (78%). When a Merck precoated silica gel F254 thin layer plate, layer thickness 0.25 mm, is developed with 1:1 (v/v) ethyl acetate-hexane and visualized with ultraviolet light, the phosphoramidate appears at  $R_f$  0.3. Thus the crude oil contained about 15 g of the phosphoramidate.
6. This procedure is designed primarily to remove phenol.

## 3. Discussion

Cycloundecanecarboxylic acid has been prepared by the bromination of cyclododecanone followed by the Favorskii rearrangement of 2-bromocyclododecanone.<sup>4</sup>

The present preparation illustrates a general and convenient method for ring contraction of cyclic ketones.<sup>5</sup> The first step is the usual procedure for the preparation of enamines. The second step involves 1,3-dipolar cycloaddition of diphenyl phosphorazidate to an enamine followed by ring contraction with evolution of nitrogen. Ethyl acetate and tetrahydrofuran can be used as a solvent in place of toluene. Pyrrolidine enamines from various cyclic ketones smoothly undergo the reaction under similar reaction conditions. Diphenyl (cycloalkyl-1-pyrrolidinylmethylene)phosphoramidates with 5, 6, 7, and 15 members in the ring have been prepared in yields of 68–76%.

The third step is hydrolysis of the *N*-phosphorylated amidines, which is carried out by either acid or alkali depending on the substrate.

Similar reaction sequences can be used successfully to convert alkyl aryl ketones to  $\alpha$ -arylalkanoic acids.<sup>6</sup>

---

## References and Notes

1. Faculty of Pharmaceutical Sciences, Nagoya City University, Nagoya 467, Japan.
2. Natelson, S.; Gottfried, S. *Org. Synth., Coll. Vol. III* **1955**, 381.

3. Shioiri, T.; Yamada, S. *Org. Synth., Coll. Vol VII* **1990**, 206.
  4. Ziegenbein, W. *Chem. Ber.* **1961**, 94, 2989.
  5. Yamada, S.; Hamada, Y.; Ninomiya, K.; Shioiri, T. *Tetrahedron Lett.* **1976**, 4749.
  6. Shioiri, T.; Kawai, N. *J. Org. Chem.* **1978**, 43, 2936.
- 

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

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

diethyl ether (60-29-7)

sodium bicarbonate (144-55-8)

phenol (108-95-2)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

ethylene glycol (107-21-1)

sodium azide (26628-22-8)

Tetrahydrofuran (109-99-9)

pyrrolidine (123-75-1)

boron trifluoride etherate (109-63-7)

hydrogen azide

cyclododecanone (830-13-7)

ethyl acetate-hexane (2639-63-6)

diphenyl phosphorochloridate (2524-64-3)

Cycloundecanecarboxylic acid (831-67-4)

Diphenyl phosphorazidate (26386-88-9)

diphenyl (cycloundecyl-1-pyrrolidinylmethylene)phosphoramidate (62914-02-7)

phosphoramidate

2-bromocyclododecanone

1-(N-Pyrrolidino)-1-cyclododecene (25769-05-5)