



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.

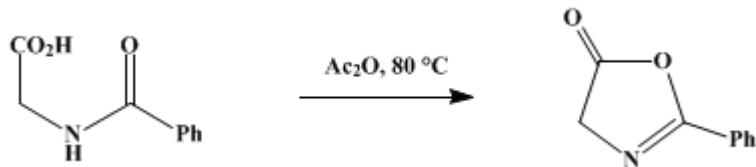
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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2-PHENYL-5-OXAZOLONE

[2-Phenyl-2-oxazolin-5-one]



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1. Procedure

A mixture of 537 g. (3 moles) of **hippuric acid** (Note 1) and 1.6 l. (17 moles) of **acetic anhydride** is prepared in a 3-l. three-necked, round-bottomed flask fitted with a sealed stirrer, a reflux condenser with a drying tube, a thermometer, and a nitrogen inlet tube (Note 2).

In a **nitrogen** atmosphere the reaction mixture is heated to 80° *on a water bath* over a period of 40 minutes with stirring. The solids slowly dissolve, and a yellow-orange solution results (Note 3). The reaction mixture is cooled to 5°, and the reflux condenser is turned downward for distillation. The condenser is cooled with a circulating fluid maintained at -20° to -40° (Note 4). The receiver is immersed in dry ice and **acetone**. At 1-3 mm. pressure, 1.5 l. of distillate is collected while the distillation flask is kept in a water bath maintained at 50° (Note 5). A capillary tube is used to bubble **nitrogen** through the reaction mixture to ensure good agitation. The distillation residue is dissolved in 1 l. of **t-butanol**, the solution scratched to encourage crystallization, and it is refrigerated overnight. The crystals are collected by filtration (Note 2). The filter cake is washed with a minimum volume of **t-butanol** and then with **Skellysolve B** (Note 6) or **hexane**. The moist cake is slurried with **Skellysolve B** or **hexane** under a **nitrogen** atmosphere (Note 7), filtered, and dried to constant weight under vacuum at ambient temperature. The yield of light buff to yellow crystals, m.p. 89-92°, is 320-328 g. (66-68%).

2. Notes

1. The checkers ran the reaction on one-fifth scale.
2. Exposure to air produces a pink to red product of lower melting point and purity.
3. Temperature control is important in order to obtain a high yield of light-colored product. Prolonged heating at 80° is to be avoided.
4. **Acetone**, cooled by passing through a copper coil placed in a dry ice-acetone bath, may be circulated through the condenser. If a temperature lower than -40° is used, the distillate will freeze in the condenser.
5. This distillate should be collected within about 1 hour, as longer distillation time diminishes the yield.
6. A saturated hydrocarbon fraction, b.p. 60-71°, available from, the Skelly Oil Company, Kansas City, Missouri.
7. Alternatively, the moist cake may be recrystallized by dissolving in hot **t-butanol** (about 800 ml.) and diluting with **Skellysolve B**. The yield is then about 40-50% and the melting point about the same as that of the reslurried product.

3. Discussion

This procedure is a modification of the original method of preparation of **2-phenyl-5-oxazolone**³ which has since appeared in the literature in various forms.^{4,5,6} In addition to the use of **acetic anhydride**, the cyclization of **hippuric acid** to **2-phenyl-5-oxazolone** has been described using **phosphorus tribromide**⁷ and **N,N'-dicyclohexylcarbodiimide**.⁸

4. Merits of the Preparation

This procedure offers a reproducible method for the preparation of [2-phenyl-5-oxazolone](#), which is not commercially available. It illustrates that strict attention to detail often smooths out an erratic procedure. [2-Phenyl-5-oxazolone](#) is, of course, an important intermediate in the synthesis of α -amino acids and related materials.⁶

References and Notes

1. Research Laboratories, The Upjohn Company, Kalamazoo, Michigan.
2. University of Illinois, Urbana, Illinois.
3. J. W. Cornforth, in H. T. Clarke, J. R. Johnson, and R. Robinson, "Chemistry of Penicillin," Princeton University Press, Princeton, New Jersey, 1949, p. 778.
4. M. M. Shemyakin, S. I. Lur'e, and E. I. Rodionovskaya, *Zh. Obshch. Khim.* **19**, 769 (1949) [C.A., **44**, 1096 (1950)].
5. H. E. Carter, J. B. Harrison, and D. Shapiro, *J. Am. Chem. Soc.*, **75**, 4705 (1953).
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Appendix Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

[acetic anhydride](#) (108-24-7)

[phosphorus tribromide](#) (7789-60-8)

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

[acetone](#) (67-64-1)

[Hippuric acid](#) (495-69-2)

[hexane](#) (110-54-3)

[t-butanol](#) (75-65-0)

[N,N'-dicyclohexylcarbodiimide](#) (538-75-0)

[2-Phenyl-5-oxazolone](#),
[2-Phenyl-2-oxazolin-5-one](#) (1199-01-5)