Organic Syntheses

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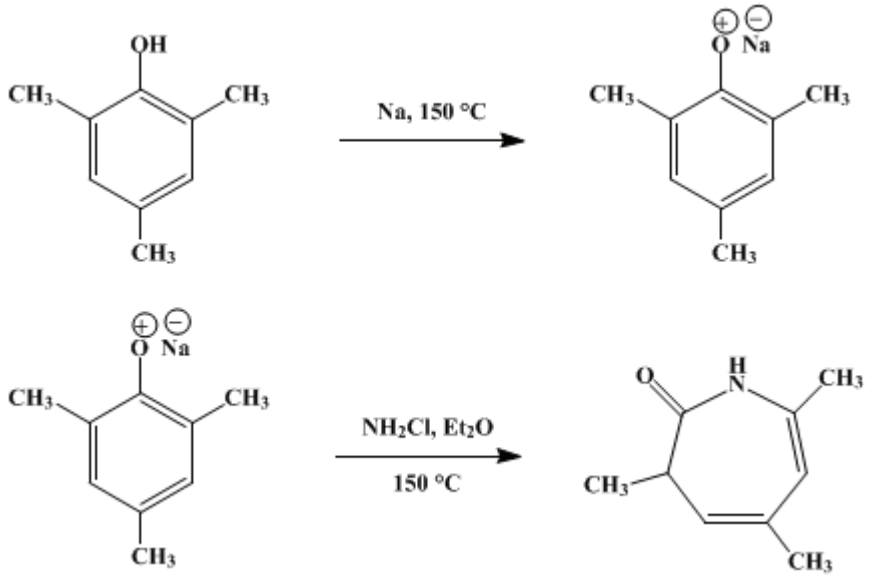
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.044.0041

Organic Syntheses, Coll. Vol. 5, p.408 (1973); Vol. 44, p.41 (1964).

1,3-DIHYDRO-3,5,7-TRIMETHYL-2H-AZEPIN-2-ONE

[2H-Azepin-2-one, 1,3-dihydro-3,5,7-trimethyl-]



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1. Procedure

Caution! Because obnoxious fumes are liberated during the reaction with chloramine, the apparatus should be set up in a well-ventilated hood.

Five hundred forty-five grams (4.00 moles) of 2,4,6-trimethylphenol (Note 1) is placed in a 1-l. three-necked flask fitted with mechanical stirrer, thermometer, 90-cm. Vigreux column, and dropping funnel (not of the pressure-equalizing variety). The Vigreux column must extend sufficiently into the top of a well-ventilated hood to entrain effectively the fumes that will be generated later in the operation. The phenol is melted with the aid of an external oil bath or Glascol® heating mantle and heated to about 100°. The heating bath is removed, and 27.6 g. (1.20 g. atoms) of sodium in cubes about 1 cm. on a side or smaller is added to the stirred mixture at such a rate that the temperature does not exceed 150–160°. The molten mass gradually becomes dark red in color as the sodium dissolves. While the addition and solution of the sodium is proceeding, a cold solution of about 0.25 mole of chloramine in 250 ml. of ether is prepared (Note 2).

When all the sodium has dissolved, the phenoxide-phenol mixture is heated to 150°. With the oil bath or heating mantle still surrounding the flask, *and with a protective shield between the reaction vessel and the operator* (Note 3), the cold ethereal chloramine solution is added with rapid stirring in a thin stream from the dropping funnel at such a rate that the temperature of the reaction mixture does not drop below 125°. Best results are obtained if the thin stream of ether solution can be added directly to the molten mass without first touching the walls of the flask.

When the addition is completed, the heat source is removed and the dark-colored contents are allowed to cool until another 0.25 mole of ethereal chloramine has been prepared and is ready for use; a wait of 1.5–2 hours between chloramine additions is convenient but not essential to the success of the experiment. The cooled reaction mixture is then reheated to 150°, and the process is repeated. This sequence is repeated until a total of four 0.25-mole portions of chloramine are added.

The reaction mixture is allowed to cool. The dropping funnel, thermometer, and Vigreux column are replaced with a stopper and short-path distillation head. The mixture is stirred while the excess phenol is removed by distillation at water-aspirator pressure; b.p. 105–110° (14 mm.). When the temperature begins to rise above 110° (14 mm.), the distillation is stopped and the residue is allowed to cool (Note 4).

Water (500 ml.) and 500 ml. of ether are added to the residue, and the mixture is well stirred. The mixture is transferred to a 2-l. separatory funnel, and the two layers are carefully separated. The aqueous layer is extracted with two additional 250-ml. portions of ether. The combined organic layers are washed twice with 5% sodium hydroxide solution and then with water, dried over anhydrous magnesium sulfate, filtered, and evaporated on a rotary evaporator. The dark residue is transferred to a distillation flask and distilled through a 30-cm. Vigreux column to yield a crystalline fraction, b.p. 130–155° (13 mm.) (Note 5). Recrystallization of this distillate from ligroin gives 68–80 g. (45–53%, based on chloramine added) of 1,3-dihydro-3,5,7-trimethyl-2H-azepin-2-one as a fluffy white solid, m.p. 131–132°.

2. Notes

1. Suitable material is obtainable from the Aldrich Chemical Co., Milwaukee, Wisconsin.
2. The ethereal chloramine solution is conveniently prepared in this quantity according to the precise directions of Coleman and Johnson.[2] It is essential to the success of this reaction that their procedure be followed exactly.
3. The protective shield is recommended despite the fact that no fire or explosion has been observed in well over fifty such experiments by the submitter.
4. The phenol recovered at this stage is reusable in subsequent preparations.
5. It is not always necessary to distil the residue. The checkers obtained a tan crystalline residue that was recrystallized from about 2 l. of heptane to give 68 g. of colorless azepinone, m.p. 130–132°. An additional 12 g. of the azepinone with the same appearance and melting point was obtained by concentrating and cooling the heptane filtrate.

3. Discussion

1,3-Dihydro-2H-azepin-2-one has been prepared in a lengthy five-step sequence by Vogel and Erb.[3] The present method,[4] the reaction of sodium 2,6-dialkylphenoxides with chloramine, easily affords the corresponding dihydroazepinones in good yield.

4. Merits of the Preparation

This reaction can be generally applied with equal success to other 2,6-dialkylphenols,[4] many of which are commercially available. Although the procedure cannot be extended to phenol or *o*-monosubstituted phenols (aminophenols result[5]), it represents a facile synthetic method for obtaining a ring system heretofore relatively unavailable. The dihydroazepinones in turn are excellent starting materials for the preparation of other novel heterocyclic systems such as 2,3-dihydro-1H-azepines,[6] 2-substituted-3H-azepines,[7] and derivatives of 2-azabicyclo[3.2.0]hept-6-ene.[8]

References and Notes

1. Research Laboratories of the Upjohn Company, Kalamazoo, Michigan. Present address: Department of Chemistry, The Ohio State University, Columbus, Ohio.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

ligroin

ether (60-29-7)

sodium hydroxide (1310-73-2)

phenol (108-95-2)

sodium (13966-32-0)

magnesium sulfate (7487-88-9)

heptane (142-82-5)

chloramine (10599-90-3)

1,3-DIHYDRO-3,5,7-TRIMETHYL-2H-AZEPIN-2-ONE,
2H-Azepin-2-one, 1,3-dihydro-3,5,7-trimethyl- (936-85-6)

2,4,6-trimethylphenol (527-60-6)

1,3-Dihydro-2H-azepin-2-one

2-azabicyclo[3.2.0]hept-6-ene