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.

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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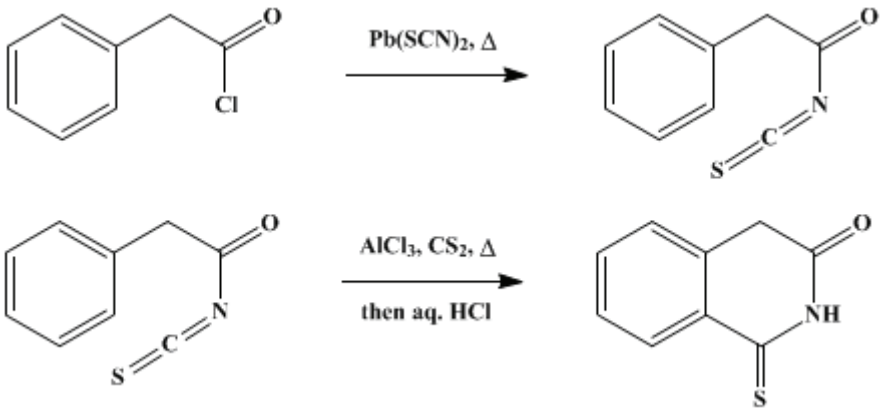
2*a*-THIOHOMOPHTHALIMIDE

[3(2H)-Isoquinolone, 1,4-dihydro-1-thioxo-]



Submitted by P. A. S. Smith and R. O. Kan[1].
Checked by Melvin S. Newman and R. L. Childers.

1. Procedure

A. *Phenylacetyl isothiocyanate*. Twenty-five grams (0.16 mole) of phenylacetyl chloride (Note 1), 100 ml. of benzene, and 53 g. (0.16 mole) of lead thiocyanate (Note 2) are placed in a 1-l., three-necked, round-bottomed flask equipped with a mechanical stirrer and a reflux condenser. The stirrer is started and the mixture is refluxed for 5 hours. A small amount of activated charcoal is added, and refluxing is continued for 5 minutes. The warm mixture is filtered through a Büchner funnel under suction (Note 3), and the solid on the filter is washed with two 50-ml. portions of benzene. The solvent is removed from the filtrate under reduced pressure, and the residue is distilled at once to yield 17.5–22.7 g. (61–79%) of phenylacetyl isothiocyanate, b.p. 83–91° at about 0.3 mm. It is a colorless liquid that rapidly darkens on standing (Note 4) and (Note 5).

B. *2a-Thiohomophthalimide*. In a 500-ml., three-necked, round-bottomed flask equipped with a mechanical stirrer, a reflux condenser, and a dropping funnel are placed 150 ml. of carbon disulfide (Note 6) and 29.3 g. (0.22 mole) of anhydrous powdered aluminum chloride. The stirrer is started, and 17.7 g. (0.10 mole) of phenylacetyl isothiocyanate is added dropwise at such a rate that the solvent refluxes gently. The total addition time is about 5 minutes. The mixture is refluxed gently for 2 hours (Note 7) and is cooled in an ice bath and treated with a solution of 10 ml. of 12*N* hydrochloric acid in 90 ml. of water; the addition is dropwise at first, more rapid later. Stirring is continued at room temperature for another hour. Crude 2*a*-thiohomophthalimide is collected by filtration on a 10-cm. Büchner funnel and is pressed dry and subsequently dried thoroughly, either in a vacuum desiccator or in an oven at 40–45° *(Caution! (Note 8)*). A solution of the imide in 300 ml. of boiling glacial acetic acid is boiled a few minutes with a small amount of activated charcoal, and the hot solution is filtered through a large fluted filter as rapidly as possible to prevent premature crystallization on the filter. Orange-yellow crystals of 2*a*-homophthalimide precipitate when the filtrate is cooled. They are separated by filtration and dried in an oven or a vacuum desiccator; weight 9.2–13.3 g. (52–75%); m.p. 221–222°.

2. Notes

1. Eastman Kodak Company white label grade of phenylacetyl chloride was used, but equally good results are obtained with the crude acid chloride obtained by treating phenylacetic acid with an excess of thionyl chloride and removing the latter under reduced pressure.
2. Lead thiocyanate was made by stirring together a solution of 45 g. (1.37 moles) of lead nitrate in 360 ml. of boiling water with a solution of 266 g. (2.74 moles) of potassium thiocyanate in 140 ml. of

boiling water. The mixture was cooled to room temperature, and 437 g. (99%) of lead thiocyanate was separated by filtration and air-dried.
3. If the filtrate is not clear, filtration should be repeated through the same filter.
4. When large quantities are used, the distillation should be performed in parts, for on prolonged heating phenylacetyl isothiocyanate decomposes with a heavy loss in yield.
5. The distillation should be carried out just before commencing Part B.
6. *sym*-Tetrachloroethane may be substituted for carbon disulfide. In this case 5 minutes of heating on a steam bath, or even no heating at all, gives satisfactory results, although the product is of slightly lower purity. The solvent may be removed quickly by steam distillation of the reaction mixture after addition of dilute acid, and the product is isolated by filtration of the slurry remaining in the flask.
7. The best heating device has been found to be an infrared lamp placed about 20 cm. from the vessel.
8. Drying at higher temperatures can be dangerous because of the low flash-point of carbon disulfide.

3. Discussion

The only reported method of preparation of 2*a*-thiohomophthalimide is by the reaction described here.[2]

4. Merits of the Preparation

This is a general method of converting arylcarbonyl and arylacetyl isothiocyanates to the corresponding thioimides as the following examples show (percent yield and duration of the reaction follow each example): 6-methyl-1*a*-thiophthalimide[2] (45%, 4 days); 4,6-dimethyl-1*a*-thiophthalimide[2] (64%, 24 hours); 5-methyl-2*a*-thiohomophthalimide (42%, 4 hours); 4-methyl-2*a*-thiohomophthalimide (48%, 4 hours); 5-methoxy-2*a*-thiohomophthalimide (41%, 4 hours); 4-chloro-2-thiohomophthalimide (40%, 4 hours); 1*a*-phenyl-2*a*-thiohomophthalimide (40%, 30 minutes); 1*a*-thio-1,2-naphthalimide[2] (25%, 4 days); 2*a*-thio-1-homo-1,2-naphthalimide[2] (41%, 16 hours); thiophene-2*a*-thio-2,3-dicarboximide (12%, 24 hours).

The thioimides can be hydrolyzed to the corresponding dicarboxylic acids.[3] The thioimides can be converted to the corresponding imides, and thiohomophthalimides can be converted to phthalimides; both conversions are one-step processes.[4] Thus a variety of substituted phthalic and homophthalic acids and their derivatives are available from these thioimides.

Thiohomophthalimides can be reduced to tetrahydroisoquinolines.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 612

References and Notes

1. Department of Chemistry, University of Michigan, Ann Arbor, Michigan.
2. P. A. S. Smith and R. O. Kan, *J. Am. Chem. Soc.*, **82**, 4753 (1960).
3. P. A. S. Smith and R. O. Kan, this volume, p. 612.
4. P. A. S. Smith and R. O. Kan, *J. Am. Chem. Soc.*, **83**, 2580 (1961).

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

sym-Tetrachloroethane

4-chloro-2-thiohomophthalimide

2a-thio-1-homo-1,2-naphthalimide

thiophene-2a-thio-2,3-dicarboximide

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

thionyl chloride (7719-09-7)

aluminum chloride (3495-54-3)

lead nitrate (10099-74-8)

Phenylacetic acid (103-82-2)

carbon disulfide (75-15-0)

potassium thiocyanate (333-20-0)

phenylacetyl chloride (103-80-0)

2a-homophthalimide

3(2H)-Isoquinolone, 1,4-dihydro-1-thioxo-,
2a-Thiohomophthalimide (938-38-5)

Phenylacetyl isothiocyanate (29313-32-4)

1a-thio-1,2-naphthalimide

lead thiocyanate

6-methyl-1a-thiophthalimide

4,6-dimethyl-1a-thiophthalimide

5-methyl-2a-thiohomophthalimide

4-methyl-2a-thiohomophthalimide

5-methoxy-2a-thiohomophthalimide

1a-phenyl-2a-thiohomophthalimide