Organic Syntheses

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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.

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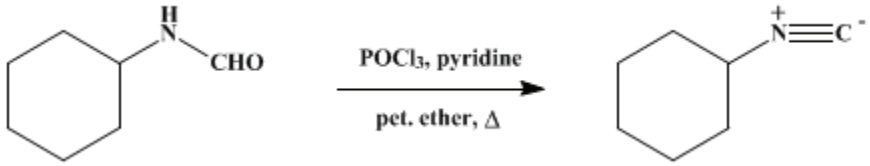
Organic Syntheses, Coll. Vol. 5, p.300 (1973); Vol. 41, p.13 (1961).

CYCLOHEXYL ISOCYANIDE



Submitted by Ivar Ugi, Rudolf Meyr, Martin Lipinski, Ferdinand Bodesheim, and Friedrich Rosendahl[1].
Checked by B. C. McKusick and M. E. Hermes.

1. Procedure

Caution! Isocyanides should be prepared in a hood since they have pungent odors and some are known to be toxic.

A solution consisting of 127 g. (1.00 mole) of N-cyclohexylformamide (Note 1), 500 ml. (490 g., 6.2 moles) of pyridine, and 300 ml. of petroleum ether (b.p. 40–60° or 30–60°) is charged into a 2-l., three-necked, round-bottomed flask equipped with a Hershberg stirrer,[2] dropping funnel, reflux condenser, and thermometer. The flask is immersed in an ice bath, and 92 g. (0.60 mole) of phosphorous oxychloride is added from the dropping funnel to the stirred mixture in the course of 30–40 minutes. The mixture is stirred under reflux for 10 minutes after all the phosphorus oxychloride is added. The mixture is then cooled to 0–5°; this converts it to a heavy slurry. Ice water (800 ml.) is gradually added with stirring, and stirring of the cold mixture is continued until all solid material has dissolved. The organic phase is separated in a separatory funnel. The aqueous phase is extracted with three 60-ml. portions of petroleum ether, and the extracts are combined with the organic phase, which is then extracted with three 100-ml. portions of water, dried over 20 g. of magnesium sulfate, and distilled through a 40-cm. vacuum-jacketed Vigreux column (Note 2). The petroleum ether is rapidly removed under slightly reduced pressure from a bath at a temperature not exceeding 50–60°. Cyclohexyl isocyanide, a colorless foul-smelling liquid (Note 3), is collected at 56–58° /11 mm.; weight 73–79 g. (67–72%); n_D^{25} 1.4488–1.4501.

2. Notes

1. The checkers prepared N-cyclohexylformamide by slowly adding 260 g. (3.52 moles) of ethyl formate with stirring to 396 g. (4.00 moles) of cyclohexylamine in a flask immersed in an ice bath. After the exothermic reaction ceased, the solution was refluxed for 2 hours and distilled through a 25-cm. Vigreux column to give 403 g. (90%) of N-cyclohexylformamide, b.p. 137–138° /10 mm., n_D^{25} 1.4849.[3]
2. The checkers used a 50-cm. spinning-band column.[4] In order to minimize resinification of the cyclohexyl isocyanide, distillation should be as rapid as possible and the temperature in the still pot should not exceed 90°.
3. The disagreeable odor of cyclohexyl isocyanide can be removed from the equipment used in this preparation by washing it with 5% methanolic sulfuric acid solution.

3. Discussion

A variety of methods has been employed in the synthesis of cyclohexyl isocyanide[5] but the dehydration of N-cyclohexylformamide is the most favorable method.

Of the numerous dehydrating agent/base systems which have been used in the preparation of isonitriles, the phosgene/tertiary amine system seems to afford the best yields. Examples of the phosgene procedure may be found in reference [5]. The disadvantage of phosgene is its extreme toxicity and the difficulty with which it is handled by the novice. The present procedure is therefore the best

combination of convenience and safety for the preparation of aliphatic isocyanides boiling above ethyl isocyanide. (Methyl and ethyl isocyanides may be prepared by using high-boiling amines like quinoline.) It has been applied to the synthesis of the following isocyanides:[5] isopropyl (38%), *n*-butyl (61%), *t*-butyl (68%), and benzyl (56%). In preparing isopropyl isocyanide or *t*-butyl isocyanide, the petroleum ether should be of boiling point 30–35°, as otherwise it is difficult to separate these low-boiling isocyanides in the indicated yield, and, even then, substantial amounts of isocyanide are found in the petroleum ether fraction.

Aromatic isocyanides can also be prepared conveniently by the dehydration of the corresponding formamides by phosphorous oxychloride, but much better results are obtained if the reaction is done in the presence of potassium *t*-butoxide rather than pyridine.[6] The preparation of methyl isocyanide by the dehydration of N-methylformamide with *p*-toluenesulfonyl chloride and quinoline is described elsewhere in this volume.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 772
- Org. Syn. Coll. Vol. 5, 1060
- Org. Syn. Coll. Vol. 6, 232
- Org. Syn. Coll. Vol. 7, 27

[8]

References and Notes

1. Institute of Organic Chemistry, University of Munich, Munich, Germany.
2. P. S. Pinkney, *Org. Syntheses*, Coll. Vol. **2**, 117 (1943).
3. R. Wietzel, German pat. 454,459 (1928) [*chem. Zentr.*, **99, I**, 2540 (1928)].
4. R. G. Nester, *Anal. Chem.*, **28**, 278 (1956).
5. P. Hoffman, G. Gokel, D. Marquarding, and I Ugi, in I. Ugi, "Isonitrile Chemistry," Academic Press, New York, N.Y., 1971, p. 9.
6. I. Ugi and R. Meyr *this volume*, p. 1060.
7. R. E. Schuster, J. E. Scott, and J. Casanova, Jr., this volume, p. 772.
8. I. Ugi and R. Meyr, *Chem. Ber.*, **93**, 239 (1960).

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

petroleum ether

Methyl and ethyl isocyanides

sulfuric acid (7664-93-9)

Phosphorus Oxychloride (21295-50-1)

pyridine (110-86-1)

phosgene (75-44-5)

ethyl formate (109-94-4)

Quinoline (91-22-5)

benzyl (2154-56-5)

n-Butyl (2492-36-6)

magnesium sulfate (7487-88-9)

cyclohexylamine (108-91-8)

isopropyl (2025-55-0)

Ethyl isocyanide (624-79-3)

t-Butyl (1605-73-8)

Cyclohexyl isocyanide (931-53-3)

N-cyclohexylformamide (766-93-8)

phosphorous oxychloride

isopropyl isocyanide (598-45-8)

Methyl isocyanide (593-75-9)

N-methylformamide (123-39-7)

p-Toluenesulfonyl chloride (98-59-9)

t-butyl isocyanide (7188-38-7)

potassium t-butoxide (865-47-4)

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