



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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.

Organic Syntheses, Coll. Vol. 7, p.294 (1990); Vol. 64, p.39 (1986).

CONVERSION OF EPOXIDES TO β -HYDROXY ISOCYANIDES: *trans*-2-ISOCYANOCYCLOHEXANOL

[Cyclohexanol, 2-isocyanato-, *trans*-]



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1. Procedure

Caution! Trimethylsilyl cyanide is very toxic. All reactions in this sequence should be carried out in a hood.

A. [(*trans*-2-Isocyanocyclohexyl)oxy]trimethylsilane. A 100-mL, three-necked flask equipped with a reflux condenser, constant-pressure dropping funnel, magnetic stirring bar, and drying tube is charged with 20.2 g (204 mmol) of trimethylsilyl cyanide (Note 1), 60 mg (0.19 mmol) of anhydrous zinc iodide (Note 2), and 5 mL of dry methylene chloride (Note 3). The constant-pressure dropping funnel is charged with 10.0 g (102 mmol) of cyclohexene oxide (Note 4) and 5 mL of dry methylene chloride. The reaction mixture is heated to reflux and the cyclohexene oxide–methylene chloride solution is added dropwise to the refluxing reaction mixture over a 30-min period. After the addition is complete, the reaction mixture is refluxed for 4 hr and then allowed to cool to room temperature. The reaction mixture is transferred to a one-necked flask and the solvent and the excess trimethylsilyl cyanide are removed under reduced pressure on a rotary evaporator (Note 5). The residue is vacuum-distilled through a 3-in. Vigreux distillation column to yield 15.74 g (78%) of [(*trans*-2-isocyanocyclohexyl)oxy]trimethylsilane, bp 69–70°C (1.5 mm) (Note 6).

B. *trans*-2-Isocyanocyclohexanol. A 250-mL, one-necked, round-bottomed flask is charged with 13.72 g (70 mmol) of [(*trans*-2-isocyanocyclohexyl)oxy]trimethylsilane, 12.12 g (210 mmol) of potassium fluoride (Note 7), and 100 mL of methanol. The reaction mixture is stirred magnetically for 5 hr at room temperature (23°C). The methanol is removed under reduced pressure on a rotary evaporator to yield a white slurry. This slurry is added to the top of a 250-g, 60–200-mesh silica gel chromatography column and the column is eluted with 20% ethyl acetate–80% hexane solvent mixture (Note 8). The solvent is removed from those fractions containing the product under reduced pressure on a rotary evaporator to afford an oil that is redissolved in methylene chloride, and the solution is filtered. The methylene chloride is removed from the filtrate under reduced pressure on a rotary evaporator to yield 8.46 g (68 mmol, 97%) of white, crystalline *trans*-2-isocyanocyclohexanol, mp 57.0–59.5°C (Note 9).

2. Notes

1. Trimethylsilyl cyanide was prepared shortly before use according to the procedure of Livinghouse, T. *Org. Synth., Coll. Vol. VII, 1990, 517*. The checkers used trimethylsilyl cyanide as supplied from Aldrich Chemical Company, Inc.

2. Anhydrous zinc iodide was purchased from Alfa Products, Morton Thiokol, Inc., and used without further purification. In one run the checkers used 0.25 mmol of ZnI_2 and obtained a better yield than when they used 0.19 mmol of ZnI_2 (84% yield instead of 73%).
3. Commercial methylene chloride is dried by distillation from calcium hydride prior to use.
4. Cyclohexene oxide was purchased from Aldrich Chemical Company, Inc., and was used without purification.
5. The checkers also carried out this process in a fume hood. All glassware was rinsed afterward with 10% KOH solution or rinsed with acetone and the rinses mixed with 10% KOH. The resulting KOH solutions were treated with Chlorox overnight before being discarded.
6. This pure, colorless liquid showed the following physical properties: IR (neat) cm^{-1} : 2950, 2870, 2145, 1454, 1267, 1255, 1144, 1114, 1065, 1028, 931, 894, 884, 844, and 758; 1H NMR (60 MHz, $CDCl_3/TMS$) δ : 0.17 (s, 9 H), 0.95–2.30 (br m, 8 H), 3.00–3.73 (br m, 2 H); 1H NMR (250 MHz, $CDCl_3$) δ : 0.15 (s, 9 H), 1.25 (m, 3 H), 1.56 (m, 1 H), 1.67 (m, 2 H), 1.86 (m, 1 H), 2.13 (m, 1 H), 3.28 (m, 1 H), 3.56 (m, 1 H); density 0.882 g/mL.
7. Potassium fluoride was purchased from the Fisher Scientific Company.
8. Approximately 100-mL fractions are collected. The progress of the chromatography is followed by analysis of the eluting fractions with thin-layer chromatography developed with iodine vapor. The checkers achieved equal success using 120 g of 70–230-mesh silica in a 30-mm \times 250-mm column.
9. The product showed the following physical properties: IR (KBr) cm^{-1} : 3470, 3400, 2965, 2945, 2870, 2175, 1450, 1376, 1328, 1302, 1240, 1123, 1090, 1081, 1007, 919, 856, and 851; 1H NMR (60 MHz, $CDCl_3/TMS$) δ : 0.70–2.40 (br m, 8 H), 2.85 (d, 1 H, $J = 5$), 3.00–3.90 (br m, 2 H); 1H NMR (250 MHz, $CDCl_3$) δ : 1.27 (m, 3 H), 1.56 (m, 1 H), 1.71 (m, 2 H), 2.02 (m, 1 H), 2.16 (m, 1 H), 2.35 (d, 1 H, $J = 4$), 3.30 (m, 1 H), 3.60 (m, 1 H).

3. Discussion

This method of preparation of *trans-isocyanocyclohexanol* is a version of our literature procedure.² It represents a general procedure that gives comparable yields with a wide variety of epoxides.² The method described is a new approach to the synthesis of isocyanides. Traditionally, isocyanides have been prepared by dehydration of formamides, the reaction of dihalocarbenes with primary amines, and the reaction of active halides and olefins with cyanides.^{3,4,5}

Isocyanides are useful intermediates because of their diverse reactivity.⁴ The β -hydroxy isocyanides, which are prepared readily by our general procedure, are particularly useful because of their straightforward conversion to β -amino alcohols in acids and their catalyzed cyclization to oxazolines.²

References and Notes

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3. Sandler, S. R.; Karo, W. "Organic Functional Group Preparations"; Academic Press: New York, 1972; Vol. III, pp. 179–204.
4. Ugi, I. "Isonitrile Chemistry"; Academic Press: New York, 1971.
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Appendix

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

ZnI_2

ethyl acetate (141-78-6)

methanol (67-56-1)

iodine (7553-56-2)

acetone (67-64-1)

KOH (1310-58-3)

Cyclohexene oxide (286-20-4)

methylene chloride (75-09-2)

potassium fluoride (7789-23-3)

hexane (110-54-3)

calcium hydride (7789-78-8)

zinc iodide

Trimethylsilyl cyanide (7677-24-9)

trans-2-ISOCYANOCYCLOHEXANOL (83152-97-0)

Cyclohexanol, 2-isocyanato-, trans-

[(trans-2-isocyanocyclohexyl)oxy]trimethylsilane (83152-87-8)

trans-isocyanocyclohexanol