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of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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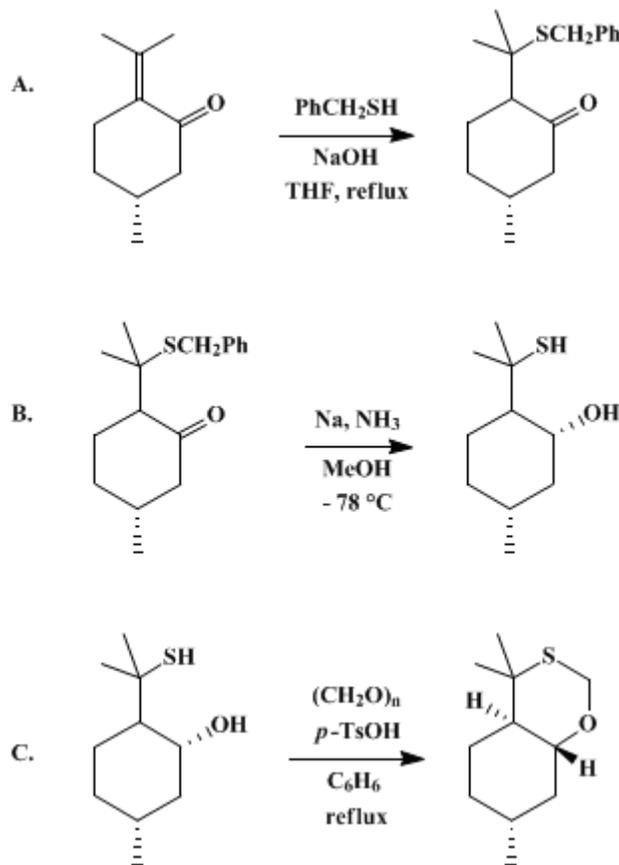
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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CHIRAL 1,3-OXATHIANE FROM (+)-PULEGONE: HEXAHYDRO-4,4,7-TRIMETHYL-4H-1,3-BENZOXATHIIN

[4H-1,3-Benzoxathiin, hexahydro-4,4,7-trimethyl-]



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1. Procedure

Caution! Benzyl mercaptan (Part A) is a foul-smelling liquid. Benzyl mercaptan, the liquid ammonia required in Part B, and the benzene employed as a solvent in Part C should be used only in a well-ventilated hood.

A. *cis- and trans-5-Methyl-2-[1-methyl-1-(phenylmethylthio)ethyl]cyclohexanone* (7-benzylthiomenthone). A 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar and a Friedrich condenser connected by its upper joint to a mineral oil bubbler through which passes nitrogen gas is charged with 500 mL of tetrahydrofuran (Note 1), 202.0 g (1.33 mol) of (+)-pulegone (Note 2), and 181.0 g (1.46 mol) of benzyl mercaptan (Note 3). The flask is flushed with nitrogen, 10 mL of aqueous 10% sodium hydroxide is added, the flask is stoppered, and the mixture is heated to reflux under a static pressure of nitrogen. After 2 hr at reflux the pale-yellow solution is allowed to cool, transferred to a 2-L separatory funnel, and washed with two 500-mL portions of saturated aqueous sodium chloride. The combined sodium chloride layers, in turn, are extracted with three 250-mL portions of ether, and the combined organic layers are dried over magnesium sulfate for 2 hr, filtered and concentrated by rotary evaporation at aspirator vacuum. The residual liquid is distilled in a good vacuum to give a fraction of bp $167\text{--}174^\circ\text{C}$ (0.4 mm) weighing 325–330 g (89–90%). The product is a

mixture of *cis* and *trans* isomers otherwise highly pure as evidenced by spectral analysis (Note 4).

B. *2-(1-Mercapto-1-methylethyl)-5-methylcyclohexanol (7-thiomenthol)*. A 5-L, three-necked, round-bottomed flask is equipped with a variable speed Hershberg stirrer and a 500-mL Dewar condenser filled with dry ice–acetone and connected by its upper joint to a mineral oil bubbler through which passes dry nitrogen gas. The flask is immersed in a dry ice–acetone bath, flushed well with nitrogen and 3000 mL of ammonia is condensed into the flask via a glass tube passed through a rubber septum in the remaining neck of the flask (Note 5). Clean sodium, 125 g (5.43 g-atom), is added slowly to the ammonia with slow stirring (Note 6). Then 250.3 g (0.906 mol) of 5-methyl-2-[1-methyl-1-(phenylmethylthio)ethyl]cyclohexanone and 72.5 mL (1.8 mol) of methanol in 625 mL of anhydrous ether (Note 7) are added dropwise via a pressure-equalized addition funnel over 5 hr to the vigorously stirred (ca. 500 rpm) solution (Note 8). Stirring is continued an additional 30 min following which 150 mL of methanol is added over 2.5 hr dropwise (to avoid a violent eruption). The solution is allowed to warm slowly (Note 9) and the addition funnel and the condenser are removed to allow the ammonia to evaporate overnight. The reaction flask is immersed in an ice bath and 700 mL of water is added cautiously over an hour to the yellow solid left by evaporation of the ammonia (Note 10). The solution is transferred to a 2-L separatory funnel and extracted with two 200-mL portions of ether, which are discarded. The aqueous layer is poured into a mixture of 500 mL of concentrated hydrochloric acid and 1000 g of ice, transferred to a 4-L separatory funnel, and extracted with four 200-mL portions of ether. The combined ether extracts are washed with 200 mL of water and 200 mL of saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated by rotary evaporation at aspirator vacuum. The residual liquid is placed under reduced pressure (0.2 mm) for 1 hr to remove the remaining solvent to give 137–140 g (80–82%) of an orange oil that is a diastereomeric mixture of which the major component constitutes 80%, as indicated by ¹³C NMR (Note 11).

C. *Hexahydro-4,4,7-trimethyl-4H-1,3-benzoxathiin*. To a 1-L, one-necked, round-bottomed flask equipped with a magnetic stirrer and charged with 325 mL of benzene (Note 12) is added 140.0 g (0.753 mol) of 5-methyl-2-(1-methyl-1-thioethyl)cyclohexanol, 26.0 g (0.87 mol) of paraformaldehyde (Note 13) and 1 g of *p*-toluenesulfonic acid monohydrate (Note 14). The flask is fitted with a Dean–Stark trap and a Friedrich condenser and the contents are refluxed for 4 hr, by which time the benzene distillate is clear. After the solution is cooled, 5 g of anhydrous potassium carbonate is added and the solution is stirred overnight, filtered, and concentrated by rotary evaporation and the residual liquid is distilled in a good vacuum to give a fraction of bp 69–94°C (0.1 mm), which weighs 130–134 g (86–89%) (Note 15). This fraction is dissolved in 250 mL of pentane, cooled to –25°C, and seeded with a crystal of the product (Note 16). Crystallization is allowed to proceed in a freezer, and collection and concentration of the mother liquor to half the original volume are carried out every other day to yield, after four crops of crystals are collected, 55–60 g (37–40%) of the spectrally pure product (Note 17).

2. Notes

1. Tetrahydrofuran was gold label from Aldrich Chemical Company, Inc.
2. (+)-Pulegone was obtained from SCM Corporation, Jacksonville, FL or Givaudan Corporation, Clifton, NJ; the specific rotation ranged from +21.85 to 22.6°. The material is also available from Aldrich Chemical Company, Inc. Pure pulegone has² $[\alpha]_D^{23} + 22.5^\circ$. The discrepancy, if any, is probably due to chemical impurities since the pulegone used has been shown to be enantiomerically pure.^{3,4} The checkers used (+)-pulegone from Givaudan Corporation, $[\alpha]_D^{20} + 25.7^\circ$, which was 94.4% pure (GLC) and contained 4.8% of isopulegone or carvone.
3. Benzyl mercaptan was used as received from Aldrich Chemical Company, Inc.
4. Spectral data; IR (film), cm^{-1} : 1708, 1620, 1500, 1458, 1382, 1363, 1120, 710, 695; ¹³C NMR (50 MHz, CDCl₃) δ : 22.2, 23.8, 27.8, 29.6, 33.1, 34.5, 36.6, 48.0, 52.3, 57.8, 126.8, 128.4 (2 C), 128.9 (2 C), 138.7, and 210.2; ¹H NMR (200 MHz, CDCl₃) δ , partial: singlets at 1.38, 1.60, and 3.73, and an intense doublet at 0.97 ($J = 5.9$). The checkers noted that the product distillate was a pale-blue color, which turned pale yellow after a few minutes.
5. The submitters noted that at least 15 kg of dry ice was required for a reaction of this scale. Using the described apparatus the checkers found that the condensation of the ammonia required 8–10 hr, which could be reduced to ca. 5 hr by using the following assembly. An over-dried, 5-L, three-necked, round-bottomed flask was equipped with a glass stirrer shaft fitted with a sleeve joint and a large Teflon blade

and the shaft was connected to an overhead motor drive. The flask was also connected to two 450-mL Dewar condensers with a large soda-lime drying tube attached to the tube connector of one condenser while the tube connector of the other condenser was attached with Tygon tubing that led through a tower of solid potassium hydroxide pellets to a tank of anhydrous ammonia. While ammonia was slowly flushed through the entire assembly, the Dewar condensers were filled with dry ice–acetone, and a dry ice–acetone bath was raised to cool the vessel by immersion. The ammonia flow rate was increased to condense ca. 3000 mL of ammonia into the flask. The condenser with the inlet connection from the ammonia was removed and the flask sealed with a glass stopper.

6. Sodium was stored under mineral oil and washed with pentane before use. For convenience the checkers used 1/6–1/4-in. sodium spheres (Matheson Coleman and Bell) that were weighed in mineral oil, then wiped free of oil, rinsed in hexane, cut in half, rinsed in hexane again, and immediately added to the reaction over a 2-hr period, during which time the dark-black mixture became extremely viscous.

7. At this point the checkers charged an oven-dried, 1000-mL pressure-equalizing addition funnel with the ketone in methanol and ether, and then quickly mounted the sealed funnel on the reaction flask by removing the flask's glass stopper.

8. Methanol was used as received from Fisher Scientific, Inc. Anhydrous ether was used as received from freshly opened containers from Mallinckrodt, Inc. and Fisher Scientific, Inc.

9. It is important to let the reaction mixture warm slowly; otherwise the ammonia will boil violently and carry some of the reaction material out of the flask.

10. This reaction is highly exothermic, and caution should be exercised since some active sodium may occasionally be left on the sides of the flask.

11. The intense ^{13}C NMR (50 MHz, CDCl_3) signals of the major isomer are at 21.9, 26.9, 29.0, 31.3, 34.5, 34.6, 45.4, 47.2, 54.6, and 72.9 ppm relative to TMS; ^1H NMR (200 MHz, CDCl_3) δ , partial: 0.91 (d, 3 H, $J = 6.5$), 1.40 (s, 3 H), and 1.52 (s, 3 H).

12. Benzene was used as received from Aldrich Chemical Company, Inc. *Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.*

13. Paraformaldehyde was used as received from Aldrich Chemical Company, Inc.

14. *p*-Toluenesulfonic acid monohydrate was used as received from Aldrich Chemical Company, Inc.

15. Excess paraformaldehyde may separate from the distillate. If this occurs, the liquid should be filtered prior to crystallization.

16. In the absence of seeding, crystallization may take several weeks. It is preferable to separate a small sample of the precursor thiomenthol from its stereoisomers by HPLC (3% ethyl acetate in hexane as eluant) and prepare a small amount of pure oxathiane from this material. Alternatively, a small amount of the product may be purified by GLC on a 5% FFAP column. The melting point of pure material is 37–38°C. The checkers, who did not have seeding crystals, found that the early crops of crystals melted when the flask was allowed to warm to ambient temperature. Consequently, the cold supernatant liquid was withdrawn from the crystals with a Pasteur pipette while the flask was maintained at ca. 0°C (ice–water bath). The crystals were subsequently recrystallized several times in the same flask without filtration. By this technique, white crystals melting at 32–35°C were obtained; this material is spectrally pure and suitable for asymmetric synthesis. The supernatant liquid was also concentrated, as the submitters described, to obtain additional crops using this technique.

17. Spectral data; IR (film), cm^{-1} : 2970–2870, 1455, 1440, 1388, 1370, 1355, 1305, 1155, 1095, 1066, 985, 955, 900, 830, and 710; ^{13}C NMR (50 MHz, CDCl_3) δ : 21.8, 22.1, 24.4, 29.4, 31.3, 34.7, 41.8 (2 C), 51.5, 67.1, 76.7 ppm; ^1H NMR (200 MHz, CDCl_3) δ partial: 0.92 (d, 3 H, $J = 6.5$), 1.27 (s, 3 H), 1.43 (s, 3 H), 3.35 (td, 1 H, $J = 10.5, 4.2$, HCO), 4.69 (d, 1 H, $J = 11.5$, SCH_2O), 5.03 (d, 1 H, $J = 11.5$, SCH_2O).

3. Discussion

Hexahydro-4,4,7-trimethyl-4*H*-benzoxathiin is used as a chiral template in the asymmetric synthesis, in over 90% enantiomeric excess, of tertiary^{3,5} and secondary⁶ α -hydroxy aldehydes, $\text{RR}'\text{C}(\text{OH})\text{CHO}$ and the derived acids, $\text{RR}'\text{C}(\text{OH})\text{CO}_2\text{H}$ and glycols, $\text{RR}'\text{C}(\text{OH})\text{CH}_2\text{OH}$.⁷ The present procedure is a slight modification of a published⁵ one.

References and Notes

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

Dry Ice

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

benzyl mercaptan (100-53-8)

TMS (16571-41-8)

carvone

1,3-OXATHIANE

(+)-PULEGONE,
pulegone (89-82-7)

7-benzylthiomenthone

2-(1-Mercapto-1-methylethyl)-5-methylcyclohexanol

7-Thiomenthol

5-methyl-2-[1-methyl-1-(phenylmethylthio)ethyl]cyclohexanone,
cis- and trans-5-Methyl-2-[1-methyl-1-(phenylmethylthio)ethyl]cyclohexanone

5-methyl-2-(1-methyl-1-thioethyl)cyclohexanol

p-toluenesulfonic acid monohydrate (6192-52-5)

isopulegone

thiomenthol

oxathiane (57917-36-9)

Hexahydro-4,4,7-trimethyl-4H-1,3-benzoxathiin,
4H-1,3-Benzoxathiin, hexahydro-4,4,7-trimethyl- (59324-06-0)

Hexahydro-4,4,7-trimethyl-4H-benzoxathiin

paraformaldehyde (30525-89-4)