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.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

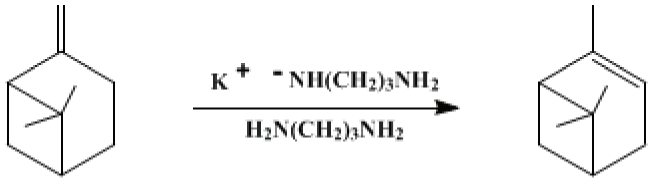
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.065.0224

Organic Syntheses, Coll. Vol. 8, p.553 (1993); Vol. 65, p.224 (1987).

(−)-α-PINENE BY ISOMERIZATION OF (−)-β-PINENE

$$KH + H_2N(CH_2)_3NH_2 \longrightarrow K^+ \ ^-NH(CH_2)_3NH_2 + H_2$$



(-) - β - pinene

(-) - α - pinene

Submitted by Charles A. Brown[1] and Prabhakav K. Jadhav[2].
Checked by Janet W. Grissom and Edwin Vedejs.

1. Procedure

Caution! Potassium hydride[3] is highly reactive toward water. Material separated from protective oil or solvent should not be exposed to air, but should be kept under argon or nitrogen.

A. *Potassium 3-aminopropylamide (KAPA).* To a bottle of 22.4% potassium hydride in oil (Note 1) is added a Teflon-covered magnetic stirring bar. The contents are agitated by first shaking and then stirring until a visually uniform dispersion is attained. Then 17.8 g (0.10 mol) of the dispersion is transferred (Note 2) to an oven-dried 250-mL flask, fitted with a magnetic stirring bar (Note 3) and (Note 4), a septum-capped inlet, and an adapter connected to a pressure-relief bubbler (mercury or oil). The apparatus is purged with dry argon or nitrogen (Note 5). The flask is charged with 100 mL of dry pentane or other volatile hydrocarbon solvent, and the contents are stirred thoroughly. The stirrer is stopped to allow the potassium hydride to settle, assisted by gentle tapping on the flask, and the supernatant liquid is drawn off with a double-ended needle under inert-gas pressure. This procedure is repeated twice to complete removal of the oil. Residual solvent is then removed in a stream of dry gas. To the dry potassium hydride powder is added rapidly 100 mL of dry 3-aminopropylamine (Note 6). *Caution! Hydrogen gas evolution.* Hydrogen evolution commences immediately (Note 7) and subsides after 1.5–2 hr. Formation of KAPA is complete at this time.

B. *(−)-α-Pinene.* Concurrently, a 3-L, three-necked, round-bottomed flask (fitted with a septum-capped adapter, gastight mechanical stirrer, and a tube adapter connected to a gas bubbler) is purged with inert gas (Note 3) and (Note 4). The flask is then charged with 1588 mL of (−)-β-pinene (Note 8). To the vigorously stirred pinene at 25°C is added the KAPA (0.1 mol) prepared in part A, using a double-ended needle, over 15 min. The reaction mixture is stirred for 24 hr at 25°C and is then quenched by addition of 100 mL of ice-cold water. The reaction mixture is transferred to a separatory funnel, washed with two 100-mL portions of water, and dried with anhydrous calcium chloride. The crude pinene is decanted from the calcium chloride through a plug of glass wool and distilled at reduced pressure from lithium aluminium hydride (Note 8) and (Note 9). The yield of (−)-α-pinene, bp 72–73°C (46 mm), $[\alpha]^{23}_{D}$ −47.45° (neat, 92% ee), is 1264 g (93%). The chemical and isomeric purity is 99% by GLC (Note 10) and (Note 11).

2. Notes

1. Potassium hydride in oil is available from Aldrich Chemical Company, Inc. and Alfa Products, Morton/Thiokol, Inc. Material from both sources has been used successfully in this preparation.
2. Potassium hydride dispersion is transferred with a 20- or 30-mL syringe fitted with a 16-gauge needle. The plunger should be lubricated with mineral oil. The density of the potassium hydride dispersion is nearly 1.0 g/mL. Alternatively, a glove box or bag may be used for direct weighing.
3. Teflon is attacked superficially by KAPA with darkening of the surface and of the solution in contact

with it. The reactivity of the KAPA is not affected. Polyethylene is not affected at all.
4. All equipment should be dried in an oven and cooled in a desiccator or under dry nitrogen.
5. From this point until the quenching of the final reaction operations must be carried out under argon or nitrogen.
6. For this reaction the amine (Aldrich Chemical Company, Inc.) from a freshly opened bottle is dried by distillation from active powdered calcium hydride. Addition over 1 min or less is required to avoid excessive foaming, which has been observed when slow or dropwise addition is used. Older samples of amine that contain water should be predried overnight with potassium hydroxide.
7. A cool (10–15°C) bath should be available to moderate the reaction if foaming occurs. Some samples of potassium hydride that have been exposed to air react sluggishly. Here application of a warm (35–40°C) bath is helpful.
8. The (−)-β-pinene used in this procedure was obtained from Glidden Organics. It was purified before use by distillation from lithium aluminium hydride; small increments of hydride were added to pinene stirred under nitrogen until an excess was present as determined by observing gas evolution on addition of a few drops of methanol to an aliquot of the slurry. The purified material had $[\alpha]_D^{23}$ −21.0° (neat, 92.1% ee). GLC analysis (10% SE-30 on Chromosorb W, 100°C) showed only one peak. Use of dry, peroxide-free pinene is critical to the success of this procedure. The (−)-β-pinene is also available from Aldrich Chemical Company, Inc. In separate experiments, (−)-β-pinene samples from Aldrich Chemical Company, Inc. and Fluka A. G. were used successfully. The checkers used Aldrich β-pinene and obtained product with $[\alpha]_D^{30}$ −46.3°.
9. Distillation from lithium aluminum hydride serves to remove completely all traces of water and amine as is required for preparation of chiral organoboranes.
10. For GLC conditions, see Note 8.
11. The reaction has been carried out at 0°C on a 0.33-mol scale using a vigorous magnetic stirrer for 4 hr.[4] Under these conditions the isomeric purity was >99.5%. Because the reaction takes place in a two-phase system, the reaction rate appears to be stirrer-dependent and vigorous agitation is essential.

3. Discussion

β-Pinene is an important auxiliary for directed chiral syntheses. It has been used for preparation of mono- and diisopinocampheylborane[5] B-allyldiisopinocampheylborane,[6] B-pinanyl-9-bora[bicyclo] nonane,[5] *cis*-pinanediol,[7] and 2-hydroxypinan-3-one.[8]

Although both enantiomers of α-pinene occur in nature, only the (+)-enantiomer is commercially available with acceptable enantiomeric purity (92–95%). The (−)-enantiomer is readily available only with 80–85% enantiomeric purity, which is impractical for use in asymmetric syntheses via organoboranes.

Fortunately, (−)-β-pinene of high enantiomeric purity (90–95%) is commercially available and can be isomerized to the thermodynamically more stable (−)-α-pinene. The isomerization has been achieved by use of several acidic, basic, and metal catalysts.[4] These methods have various limitations such as partial racemization, low chemical yields, and vigorous reaction conditions. The current procedure is based on our earlier report using KAPA at 0°C on a much smaller scale.[4] The change to 25°C from 0°C was made to simplify the reaction conditions by eliminating the need for external cooling. The reaction has also been carried out on somewhat reduced scale (1–5 mol) using a magnetic stirrer in place of the mechanical stirrer.

References and Notes

1. Chemical Dynamics Dept., IBM Research Laboratory K34-281, 5600 Cottle Road, San Jose, CA 95193.
2. Richard B. Wetherill Chemistry Laboratory, Purdue University, West Lafayette, IN 47907.
3. For a general discussion on metallation with and handling of potassium hydride, see Brown, C. A. *J. Org. Chem.* **1974**, *39*, 3913.
4. For a general discussion on methods of isomerization of β-pinene to α-pinene, see Brown, C. A. *Synthesis* **1978**, 754.

5. Brown, H. C.; Jadhav, P. K.; Mandel, A. K. *Tetrahedron* **1981**, *37*, 3547.
6. Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092.
7. Matteson, D. S.; Ray, R. *J. Am. Chem. Soc.* **1980**, *102*, 7590.
8. Yamada, S.-i.; Oguri, T.; Shioiri, T. *J. Chem. Soc., Chem. Commun.* **1976**, 136.

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

amine

(−)-α-pinene

(−)-β-PINENE

Potassium 3-aminopropylamide (KAPA)

20- or 30-mL syringe

mono- and diisopinocampheylborane

calcium chloride (10043-52-4)

methanol (67-56-1)

hydrogen (1333-74-0)

nitrogen (7727-37-9)

mercury (7439-97-6)

potassium hydroxide (1310-58-3)

hydride

Pentane (109-66-0)

lithium aluminum hydride,
lithium aluminium hydride (16853-85-3)

argon (7440-37-1)

calcium hydride (7789-78-8)

potassium hydride (7693-26-7)

α-pinene (7785-70-8)

pinene,

β-pinene (18172-67-3)

3-aminopropylamine (109-76-2)

B-allyldiisopinocampheylborane

2-hydroxypinan-3-one

cis-pinanediol