Organic Syntheses

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.*

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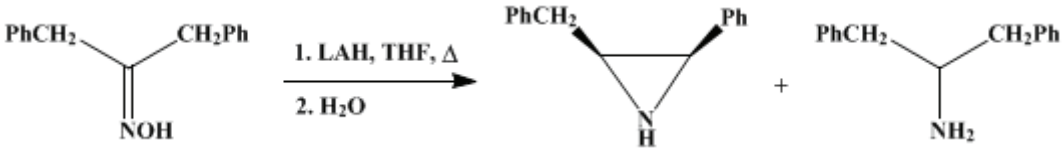
# *cis*-2-BENZYL-3-PHENYLAZIRIDINE

## [Aziridine, 2-benzyl-3-phenyl-, *cis*-]




Submitted by Katsumi Kotera and Keizo Kitahonoki[1].
Checked by Donald R. Strobach and R. E. Benson.

## 1. Procedure

In a 1-l., four-necked, round-bottomed flask fitted with a sealed mechanical stirrer, a thermometer, a dropping funnel, and a reflux condenser protected from atmospheric moisture with a drying tube containing calcium chloride are placed 350 ml. of dry tetrahydrofuran (Note 1) and 3.80 g. (0.100 mole) of powdered lithium aluminum hydride (Note 2). The slurry is stirred while a solution of 11.27 g. (0.0500 mole) of dibenzyl ketoxime (Note 3) in 80 ml. of dry tetrahydrofuran is added dropwise with cooling at 20° over a 10-minute period. The contents of the flask are gradually heated to reflux (Note 4) with stirring in an oil bath at 90° (external temperature) for 3 hours (Note 5); at *ca.* 62° the color of the mixture turns from the initial pale green to a permanent, light chocolate color (reaction may be exothermic at this point). The mixture is cooled with ice water and decomposed by gradual addition of 12 ml. of water at a temperature below 20°. The precipitate is collected by filtration, washed with 100 ml. of ether, and added to 200 ml. of ether. This mixture is stirred for *ca.* 10 minutes and filtered, and the residue is washed with 100 ml. of ether. The ethereal extracts and washings are combined with the original filtrate, dried over anhydrous sodium sulfate over-night, and concentrated with a rotary evaporator at 30° (20 mm.) to give 10.60–11.0 g. of a pale yellow oil (Note 6).

The product is dissolved in 100 ml. of petroleum ether, b.p. 30–40°, with warming, and the solution is transferred to a chromatographic column consisting of 75 g. of silica gel (Note 7). The product is eluted sequentially with (A) 300 ml. of petroleum ether, (B) 300 ml. of 3:1 (v/v) petroleum ether:benzene, (C) 300 ml. of 1:1 (v/v) petroleum ether:benzene, (D) 600 ml. of 1:3 (v/v) petroleum ether:benzene, and (E) 600 ml. of benzene. Fractions A and B are discarded (Note 8). The oil (8.50–9.15 g.) obtained by distillation of the solvent from the combined fractions C, D, and E is dissolved in 65 ml. of petroleum ether. Cooling gives 5.00–6.61 g. of colorless needles, m.p. 44–45° (Note 9). Concentration of the filtrate and cooling yield successive crops of product, m.p. 41–45°. The total yield is 7.45–8.15 g. (71–78%) (Note 9).

## 2. Notes

1. Tetrahydrofuran of laboratory chemical grade supplied by Fisher Scientific Co. was used without further purification by the checkers. The submitters used tetrahydrofuran purified by the method of *Org. Syntheses*, Coll. Vol. **4**, 259 (1963). *[Caution! See this volume, page 976, for a warning regarding purification of tetrahydrofuran.]*
2. Obtained from Metal Hydrides, Inc.
3. The submitters used oxime prepared from Tokyo Kasei G. R. grade dibenzyl ketone in the usual manner and recrystallized from ether-petroleum ether; m.p. 123–124° (yield 93%).[2] The checkers prepared the oxime in the following manner. A mixture of 50 g. (0.24 mole) of 1,3-diphenyl-2-propanone (Eastman Organic Chemicals, practical grade), 50 g. (0.72 mole) of hydroxylamine hydrochloride, 250 ml. of reagent grade pyridine, and 250 ml. of ethanol was heated under reflux for 2 hours. The solvent was removed by distillation at reduced pressure, and the residue was triturated with 250 ml. of cold water. The solid was collected by filtration and washed with a small volume of cold water. Crystallization of the moist product from ethanol gave 50.5 g. (94%) of dibenzyl ketoxime, m.p.

122–124°.
4. The internal temperature is 66°. At lower temperatures the reaction takes longer, and the yield of the aziridine is lower. The submitters found that the yield is 66% after 6 hours at a reaction temperature of 50° and 55% after 30 hours at a temperature of 20° and 44 hours at −20°.
5. The consumption of the oxime can be checked by thin-layer chromatography on silica gel G with the solvent system chloroform/methanol (95/5 v/v) and a spray reagent consisting of 5% potassium dichromate in 40% sulfuric acid. The oxime appears as an immediate dark spot and the aziridine as a yellow spot. The checkers observed identical mobilities ($R_f$ 0.8) for both compounds.
6. The submitters found that purification of the oil by direct crystallization gives only a small amount of the pure product. Attempted purification by distillation did not give satisfactory results.
7. Silica gel, particle size 0.2–0.5 mm. (Catalog No. 7733), of E. Merck A. G. (Darmstadt) was used.
8. The fractions are tested by thin-layer chromatography on silica gel G with the solvent system and spray reagent described in (Note 5).
9. The product is sufficiently pure for most purposes. The pure sample after additional recrystallizations melts at 44.7–45.1°.

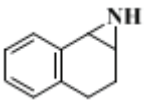
## 3. Discussion

In addition to the present method,[3,4,5] 2-benzyl-3-phenylaziridine has been obtained from O-substituted dibenzyl ketoximes,[3,5] chalcone oxime[4] and 3,5-diphenyl-2-isoxazoline[6] by a reduction similar to that described here.

## 4. Merits of the Preparation

The present preparation illustrates the general method for the synthesis of aziridines by reduction of ketoximes[3,4,5] and their O-acyl and -alkyl derivatives[3,5,6] having an aromatic ring attached to carbon α or β to the oximino function and of aldoximes[4] having the aromatic ring attached to the carbon atom β to the oximono group. It has also been applied to oximes of cyclic[3,4,7] and bridged[3,8,9,10] ring ketones, such as α- and β-tetralone, 1,2,3,4-dibenzo-1,3-cycloheptadien-6-one, and bicyclo [2.2.2] octanone and its benzo analogs. Examples of aziridines prepared by this method are given in Table I; derivatives of the products are listed in Table II. Because of the accessibility of oximes the present method provides a more convenient synthesis of several types of aziridines than do other methods.[11] Furthermore, the reaction proceeds stereoselectively to give the *cis*-substituted aziridine.[3] A review[10] of the present synthetic method including mechanistic aspects[3,5,6] is available. The effect of oxime configuration (*syn* or *anti*) has been investigated.[4,9,12] The addition of N-methyl-*n*-butylamine (*in situ*) has been found to increase the reaction rate and yield of aziridine.[10]

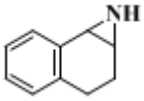
TABLE I AZIRIDINES PREPARED BY REDUCTION OF OXIMES WITH LITHIUM ALUMINUM HYDRIDE

| Parent Ketone or Aldehyde | Aziridine | M.P., °C | Yield, % |
|---|---|---|---|
| Acetophenone | 2-Phenylaziridine | (Oil)[a] | 17 |
| Phenylacetaldehyde | 2-Phenylaziridine | (Oil)[a] | 34 |
| 1-Acetonaphthone | 2-(α-Naphthyl)-aziridine | 66–67 | 64 |
| 3-Phenyl-2-butanone | 2-(α-Methylbenzyl)-aziridine | (Oil)[b] | 38 |
| 1-Tetralone |  | 52–53.5[c] | 11 |

[a]Cf. F. Wolfheim, *Ber.*, **47**, 1440 (1914); S. Gabriel and J. Colman, *Ber.*, **47**, 1866 (1914); S. J. Brois, *J. Org. Chem.*, **27**, 3532 (1962); A: Hassner and C. C. Heathcock, *Tetrahedron Letters*, 1125 (1964).
[b]Along with this formation of 2,3-dimethyl-2-phenylaziridine (oil, 10%) has been reported [G. Alvernhe and A. Raurent, *Bull. Soc. Chim. France*, 3003 (1970)].
[c]Cf. G. Drefahl and K. Ponsold, *Ber.*, **93**, 519 (1960); A. Hassner and C. Heathcock,

*Tetrahedron*, **20**, 1037 (1964).

TABLE II DERIVATIVES OF AZIRIDINES PREPARED BY REDUCTION OF OXIMES WITH LITHIUM ALUMINUM HYDRIDE

| Aziridine | 1-(Phenyl-carbamoyl) Derivative, M.P., °C | 1-(*p*-Nitrobenzoyl) Derivative, M.P., °C | Derived Thiazolidine-2-thione, M.P., °C |
|---|---|---|---|
| 2-Phenyl-aziridine | 133.5–135 | 120–122.5 | 170–171[a,b] 168–169[b,c] |
| 2-(α-Naphthyl)-aziridine | | | 235–237 (dec.) |
| 2-(α-Methylbenzyl)-aziridine | | 65–66 and 178–179[d] | 96.5–97.5 and 165.5–166[d] |
|  | 157–158 | | 188.5–190.5 |

[a]Aziridine prepared from acetophenone.
[b]Cf. C. S. Dewey and R. A. Bafford, *J. Org. Chem.*, **30**, 491 (1965).
[c]Aziridine prepared from phenylacetaldehyde.
[d]Presumably *erythro* and *threo* isomers.

## References and Notes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10. K. Kotera and K. Kitahonoki, *Org. Prep. Proced.*, **1**, 305 (1969).
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## Appendix
## Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

petroleum ether

α- and β-tetralone

1,2,3,4-dibenzo-1,3-cycloheptadien-6-one

ethanol (64-17-5)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

Acetophenone (98-86-2)

carbon (7782-42-5)

pyridine (110-86-1)

Hydroxylamine hydrochloride (5470-11-1)

potassium dichromate (7778-50-9)

aziridine (9002-98-6)

dibenzyl ketone,
1,3-Diphenyl-2-propanone (102-04-5)

phenylacetaldehyde (122-78-1)

Tetrahydrofuran (109-99-9)

1-Tetralone (529-34-0)

oximino

lithium aluminum hydride (16853-85-3)

dibenzyl ketoxime (1788-31-4)

2-benzyl-3-phenylaziridine

chalcone oxime

3,5-diphenyl-2-isoxazoline

bicyclo [2.2.2] octanone (2716-23-6)

2-Phenylaziridine,
2-Phenyl-aziridine

2-(α-Naphthyl)-aziridine

3-Phenyl-2-butanone

2-(α-Methylbenzyl)-aziridine

2,3-dimethyl-2-phenylaziridine

N-methyl-n-butylamine (110-68-9)

cis-2-Benzyl-3-phenylaziridine,
Aziridine, 2-benzyl-3-phenyl-, cis- (1605-08-9)