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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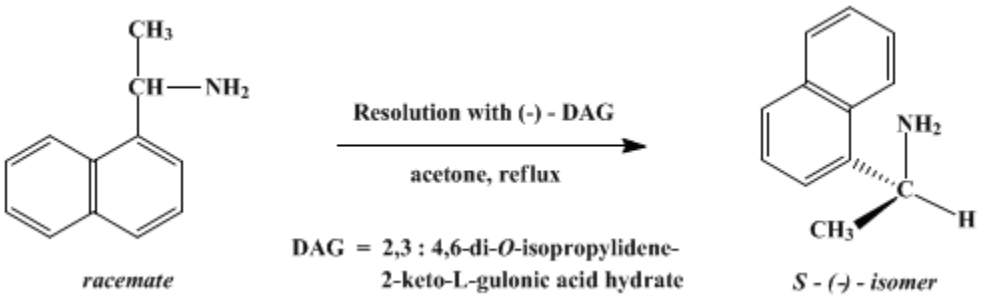
(*S*)-(−)-α-(1-NAPHTHYL)ETHYLAMINE

[(*S*)-1-Naphthalenemethanamine, α-methyl-]



Submitted by E. Mohacsi and W. Leimgruber[1].
Checked by P. E. Georghiou, J. D. Lock, Jr., and S. Masamune.

1. Procedure

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.

A. (*S*)-(−)-α-(1-*Naphthyl)ethylamine*. A mixture of 58.44 g. (0.1849 mole) of (−)-2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid hydrate [(−)-DAG] (Note 1) and 1.7 l. of acetone (Note 2) is placed in a 3-l. Erlenmeyer flask. A boiling chip is added, and the mixture is heated to a gentle boil. To the resulting hot solution is added cautiously but rapidly, over a 1-minute period, 34.24 g. (0.2002 mole) of racemic α-(1-naphthyl)ethylamine (Note 3) in 100 ml. of acetone. The mixture is allowed to stand at room temperature for approximately 4 hours. The (−)-amine (−)-DAG salt is filtered with suction, washed with 100 ml. of acetone, and dried in a vacuum oven at 60° to constant weight, yielding 73–76 g. of the crude (−)-amine (−)-DAG salt, m.p. 205–207° (dec.), (Note 4), $[\alpha]_D^{25}$ −14.2° (*c* 1.01%, methanol). The crude salt and 4.2 l. of ethanol (Note 5) are placed in a 5-l., round-bottomed flask fitted with a reflux condenser and a mechanical stirrer. The mixture is stirred and heated at reflux for about 4 hours, during which time a clear solution is obtained. The condenser is then placed in a descending position and approximately 1.4 l. of the ethanol is distilled at atmospheric pressure (Note 6), and stirring is continued (Note 7) at room temperature for about 16 hours. The purified salt is collected on a filter and dried to constant weight, yielding 36–37 g. of white needles, m.p. 216–218° (dec., (Note 4)), $[\alpha]_D^{25}$ −17.5° (*c* 1.02%, methanol). For recrystallization, the crude salt and 4.0 l. of ethanol are used. Removal of 3.0 l. of the solvent yields 33.5–33.9 g. (75–76%) of pure (−)-amine (−)-DAG salt as white needles, m.p. 219–221° (dec., (Note 4)), $[\alpha]_D^{25}$ −18.5° (*c* 0.90%, methanol).

To a slurry of 33.5–33.9 g. of the pure (−)-amine (−)-DAG salt in 130 ml. of water is added 56 ml. of 2 *N* aqueous sodium hydroxide, and the resulting oily suspension is extracted with four 80-ml. portions of diethyl ether. The combined ether extracts are washed with 50 ml. of water and dried over anhydrous magnesium sulfate. After filtration and removal of the ether on a rotary evaporator, the crude base is distilled under reduced pressure through a 20-cm. Vigreux column (Note 8), affording 10.9–11.7 g. (85–90% yield, based on the amount of the salt used) of the pure (−)-amine as a colorless liquid, b.p. 156–157° (11 mm.), n_D^{24} 1.6211–1.6212, d_4^{24} 1.056, $[\alpha]_D^{25}$ −80.1° (neat), $[\alpha]_D^{25}$ −60.4° (*c* 10.0%, methanol), $[\alpha]_D^{25}$ −59.3° (*c* 0.65%, methanol) (Note 9) and (Note 10).

B. *Recovery of* (−)-DAG. The basic aqueous solution (about 186 ml.), obtained after removal of the (−)-amine by ether extraction, is placed in a 600-ml. beaker and cooled to 0–5° with an ice bath. The solution is magnetically stirred and carefully acidified with 2 *N* hydrochloric acid at 0–5° to approximately pH 2 (Note 11). The precipitated (−)-DAG is filtered without delay (Note 12), washed

with 20 ml. of ice water, and air dried to constant weight, yielding 20.0–20.9 g. (91–94%, yield based on the amount of the salt used) of (−)-DAG, m.p. 103° (dec.), $[\alpha]_D^{25}$ −21.6° (*c* 2.28%, methanol) (Note 13) and (Note 14).

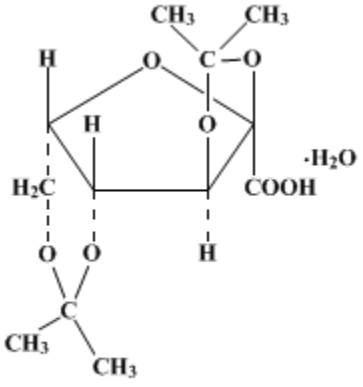
2. Notes

1. (−)-2,3:4,6-Di-*O*-isopropylidene-2-keto-L-gulonic acid hydrate [(−)-DAG] is available from the Commercial Development Dept., Hoffmann-La Roche Inc., Nutley, new Jersey 07110.
2. Mallinckrodt A.R. grade acetone was used. The checkers found that the use of 1.5 l. of acetone, as originally recommended by the submitters, resulted in an immediate precipitation of the (−)-DAG salt upon addition of the amine, inducing incomplete mixing of the two reagents.
3. Practical grade racemic α-(1-naphthyl)ethylamine (purchased from Norse Laboratories, Inc., Santa Barbara, California 93103) was distilled before use, b.p. 117–118° (2 mm.).
4. The melting point was measured in an evacuated, sealed capillary and found to deviate slightly from this value on occasion.
5. The checkers used ethanol containing a maximum of 0.1% (w/w) of water and a maximum of 0.001% (w/w) of benzene.
6. The salt begins to crystallize toward the end of this operation.
7. It is advisable to maintain stirring, avoiding the formation of lumps, thus assuring a uniform product.
8. The distillation apparatus was first flushed with nitrogen, as the amine formed a white crystalline solid on contact with atmospheric carbon dioxide.
9. Reported physical constants[2,3] of the amine are: b.p. 153° (11 mm.), d_4^{25} 1.055, $[\alpha]_D^{25}$ −80.8° (neat).
10. A 100 MHz. ^{1}H NMR spectrum ($CDCl_3$) of the amine in the presence of an equal amount of the chiral shift reagent, tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III)[4] (submitters), or in the presence of an equal amount of tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III) (checkers), revealed that the product contained no detectable enantiomeric isomer.
11. The pH was measured with a Beckman Zeromatic pH meter.
12. (−)-DAG is unstable in aqueous acid.
13. TLC of (−)-DAG on Silica Gel G using the solvent system, benzene:methanol:acetone:acetic acid (70:20:5:5), shows one spot, $R_f \sim 0.7$.
14. The reported[5] m.p. is 98–99°.

3. Discussion

(*S*)-(−)-α-(1-Naphthyl)ethylamine has been prepared by resolution of the racemic amine with camphoric acid in unspecified yield.[2,3]

The procedure presented herein allows the preparation of the same optically active amine in approximately 70% yield by the use of a new resolving agent, (−)-2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid hydrate, [(−)-DAG], whose utility for the resolution of a variety of amines has been thoroughly demonstrated.[6]



(-)-DAG

(−)-DAG is an ascorbic acid derivative with the following structure: It is an attractive resolving agent, because it is relatively inexpensive and commercially available on a ton scale for industrial applications. One of the remarkable properties of (−)-DAG, lacking in other acidic resolving agents, is its water-insolubility, which permits the recovery of the resolving agent in a simple and efficient manner.

Among the amines that have been resolved with (−)-DAG: α-phenylethylamine,[6] [(R-(R*, R*)]-2-amino-1-(4-nitrophenyl)-1,3-propanediol,[6] 1,2,3,4,5,6,7,8-octahydro-1-(4-methoxyphenylmethyl) isoquinoline,[6] 3-methoxymorphinan,[6] 1,2,3,4-tetrahydro-7-methoxy-4-phenylisoquinoline,[6] 3-hydroxy-*N*-methylmorphinan,[6] 1,2,3,4-tetrahydro-6,7-dimethoxy-1-[3,4-(methylenedioxy)phenyl]isoquinoline,[7] 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3,4,5-trimethoxyphenyl)isoquinoline,[7] 2-[4-(phenylmethoxy) phenyl]-2-(3,4-dimethoxyphenyl)ethanamine,[8] *N*-norlaudanosine,[9] and 1,2,3,4-tetrahydro-6,7-dimethoxy-1-[3-methoxy-4-(phenylmethoxy)phenyl]isoquinoline.[10]

References and Notes

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

(−)-amine

(S)-(−)-α-(1-NAPHTHYL)ETHYLAMINE

(−)-2,3:4,6-di-O-isopropylidene-2-keto-L-gulonic acid hydrate

(−)-amine (−)-DAG

(−)-2,3:4,6-Di-O-isopropylidene-2-keto-L-gulonic acid hydrate [(−)-DAG]

tris[3-(trifluoromethylhydroxymethylene)-d-camphorato]europium(III)

tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium(III)

(−)-2,3:4,6-di-O-isopropylidene-2-keto-L-gulonic acid hydrate, [(−)-DAG]

N-norlaudanosine

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

acetone (67-64-1)

magnesium sulfate (7487-88-9)

α-Phenylethylamine (3886-69-9)

α-(1-naphthyl)ethylamine

camphoric acid

1,2,3,4,5,6,7,8-octahydro-1-(4-methoxyphenylmethyl)isoquinoline

1,2,3,4-tetrahydro-6,7-dimethoxy-1-[3,4-(methylenedioxy)phenyl]isoquinoline

1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3,4,5-trimethoxyphenyl)isoquinoline

2-[4-(phenylmethoxy)phenyl]-2-(3,4-dimethoxyphenyl)ethanamine

1,2,3,4-tetrahydro-6,7-dimethoxy-1-[3-methoxy-4-(phenylmethoxy)phenyl]isoquinoline

(S)-1-Naphthalenemethanamine, α-methyl- (10420-89-0)

3-hydroxy-N-methylmorphinan (125-73-5)

3-methoxymorphinan

1,2,3,4-tetrahydro-7-methoxy-4-phenylisoquinoline