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.

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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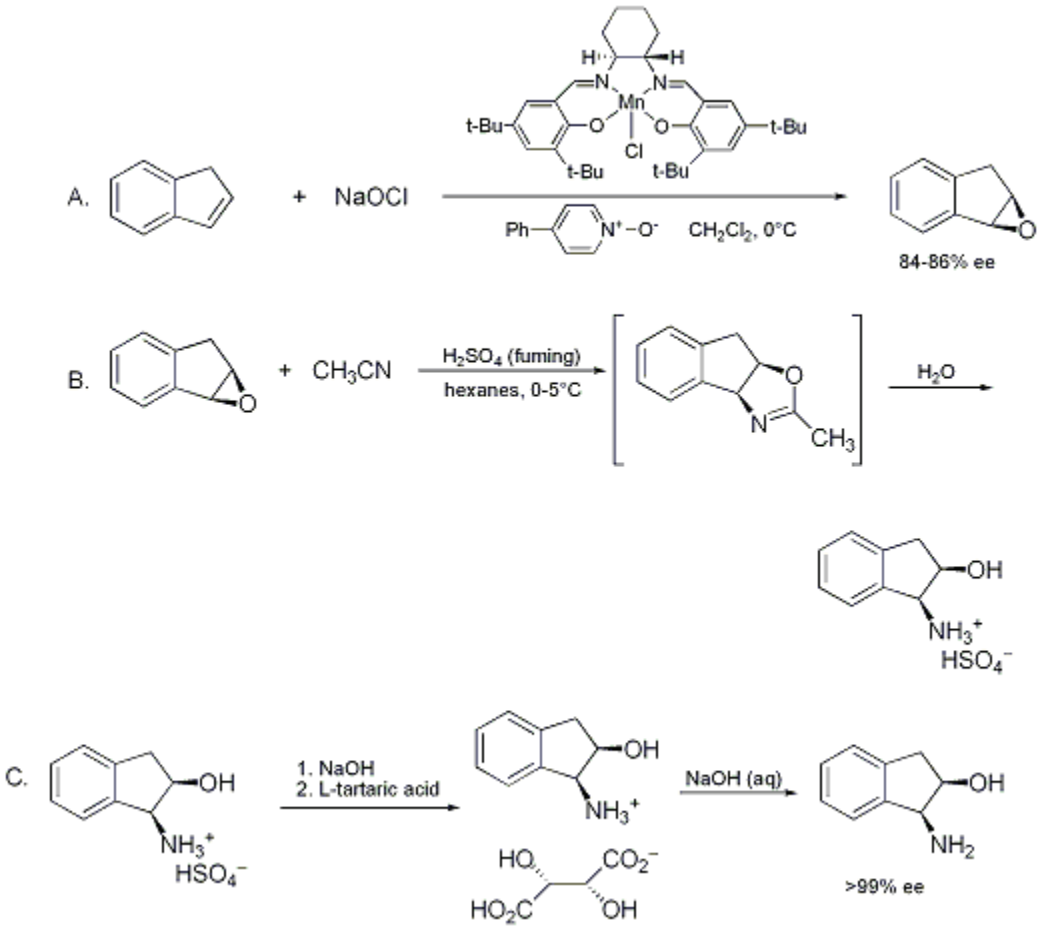
(1S,2R)-1-AMINOINDAN-2-OL

[1H-Inden-2-ol, 1-amino-2,3-dihydro-(1S-cis)-]



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1. Procedure

A. (1S,2R)-Indene oxide . A 500-mL, three-necked, round-bottomed flask equipped with an overhead mechanical stirrer, a 125-mL addition funnel, and a thermocouple is charged with indene ((Note 1), 29.0 g, 0.25 mol, 1 equiv), dichloromethane (CH_2Cl_2) (30 mL), (S,S)-(N,N')-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride (0.953 g, 1.5 mmol, 0.6 mol% , (Note 2)), and 4-phenylpyridine N-oxide ((Note 3), 1.28 g, 7.5 mmol, 3.0 mol%) under a nitrogen (N_2) atmosphere. The resulting brown mixture is cooled to −5°C, and then a cold sodium hypochlorite (NaOCl) solution (191 mL, 1.7 M, 1.3 equiv, (Note 4)) is added slowly with vigorous stirring while maintaining the reaction temperature between 0°C and 2°C (Note 5). Upon complete addition of the bleach, the reaction is stirred for an additional 1 hr at 0°C. At this point, hexanes (200 mL) are added in one portion with stirring, and the reaction mixture is filtered through a pad of Celite on a large Büchner funnel. The filter cake is washed with dichloromethane (2 × 50 mL), and the filtrate is transferred to a 500-mL separatory funnel. The lower aqueous layer is removed, and the brown organic layer is washed with aqueous saturated sodium chloride (NaCl) solution (100 mL). The organic layer is dried over sodium sulfate (Na_2SO_4), filtered, and concentrated by rotary evaporation. A small amount of calcium hydride (CaH_2) (100 mg) is added to the brown residue, and the epoxide is isolated by short path

vacuum distillation, bp 58-60°C (0.025 mm), to yield 24.0 g of epoxyindane (84-86% ee) as a colorless to slightly yellow liquid (0.197 mol, 71% yield, (Note 6), (Note 7), and (Note 8)).

B. (1S,2R)-1-Aminoindan-2-ol (crude). A dry, 1000-mL, three-necked, round-bottomed flask equipped with a large magnetic stir bar, a 250-mL addition funnel, a 50-mL addition funnel, and a thermocouple is charged with dry acetonitrile (100 mL , (Note 9)) and cooled to −5°C under a N_2 atmosphere. The mixture is stirred vigorously, and slow addition of fuming sulfuric acid (20 mL, 0.4 mol, 2 equiv, 27-33% SO_3, (Note 10)) is begun, followed by dropwise addition of a solution of the epoxide (26.0 g, 0.197 mol) in dry hexanes (200 mL, (Note 9)) . The reagents are added simultaneously at a rate such that the reaction temperature is maintained between 0 and 5°C. After the additions are complete, the reaction mixture is warmed to room temperature and stirred for 1 hr. Water (100 mL) is added via the addition funnel over 10-15 min, and the resulting biphasic mixture is stirred for an additional 30 min. The lower aqueous phase is separated, diluted with 100 mL of water and concentrated by distillation at atmospheric pressure to a head temperature of 100°C. The mixture is heated at reflux for 3 hr, after which time the mixture is cooled to room temperature. The crude aqueous solution of aminoindanol is used without further purification in the next step (Note 11).

C. (1S,2R)-1-Aminoindan-2-ol (100% ee). A 500-mL, three-necked, round-bottomed flask equipped with a large magnetic stir bar, a 125-mL addition funnel, a pH probe, and a thermocouple is charged with the hydrolysis solution from Part B and 1-butanol (100 mL). Sodium hydroxide (80 mL of an aqueous 50% solution, (Note 12)) is added slowly with external ice bath cooling to maintain the temperature below 30°C until the reaction mixture reaches a pH of 12-13. The upper 1-butanol layer is separated, and the aqueous layer is extracted with another 100 mL of 1-butanol . The combined butanol extracts are diluted with methanol (200 mL), and vacuum-filtered through a Büchner funnel into a 2000-mL, three-necked, round-bottomed flask equipped with a mechanical overhead stirrer, 250-mL addition funnel, and reflux condenser. The reaction mixture is stirred vigorously and heated to reflux, and a solution of L-tartaric acid (35.5 g, 0.24 mol, 1.2 equiv) in methanol (200 mL) is added over 15-30 min while reflux is maintained. Heating is discontinued until a thick but stirrable slurry is formed (Note 13). The suspension is reheated to reflux for 2 hr (Note 14). At this point, the mixture is cooled to room temperature and allowed to stand for 1 hr. The resulting solids are collected on a Büchner funnel and washed with methanol (2 × 100 mL). The white solid thus obtained is then dried under reduced pressure to yield 47.4 g of the 1:1 tartrate salt (Note 15).

A 300-mL, three-necked, round-bottomed flask equipped with a large magnetic stir bar, a 125-mL addition funnel, a pH probe, and a thermocouple is charged with the aminoindanol-tartrate salt. Water (95 mL, 2:1 v/w) is added, and the mixture is stirred under a N_2 atmosphere. Aqueous sodium hydroxide (50 wt-%, 23 mL, 2 equiv, (Note 12) and (Note 16)) is added with external ice bath cooling until the reaction mixture reaches pH 12-13, resulting in precipitation of the aminoindanol free base. The mixture is cooled to 0°C and allowed to stand at that temperature for an additional 30 min. The white to tan solid is collected by vacuum filtration, washed with ice-cold water (20 mL), and air-dried on the filter. The solid is dissolved in hot toluene (1:10 w/v, (Note 17)), and the resulting solution is allowed to cool to room temperature, then further cooled to 4°C for 1 hr. The resulting white solid is collected by vacuum filtration, washed with cold toluene (20 mL), and dried under reduced pressure. The total yield of aminoindanol (100% ee, (Note 18)) is 17.2 g, mp 122-124°C (Note 19).

2. Notes

1. Technical grade indene (92%) was obtained from Aldrich Chemical Company, Inc. , and was passed through a 10 × 10-cm column of basic alumina to remove highly colored impurities. The compound was then distilled under a N_2 atmosphere from a small amount of CaH_2. The distillate was stored under N_2 at 4°C.
2. The epoxidation catalyst was prepared according to the published procedures.[5] [6] Alternatively, research quantities can be purchased from Aldrich Chemical Company, Inc., or bulk quantities can be purchased from ChiRex Ltd, Dudley, UK.
3. 4-Phenylpyridine N-oxide was purchased from Aldrich Chemical Company, Inc., and used as received. Other pyridine N-oxide derivatives have been used with success in the epoxidation reaction. The choice of the pyridine N-oxide derivative has been demonstrated to have a small yet measurable

impact on both the rate of reaction and the enantiomeric excess of the product epoxide.[7] [8] [9]
4. Commercial 10-13% NaOCl was purchased from Aldrich Chemical Company, Inc. , and stored at 4° C. The concentration of bleach was determined according to the method of Kolthoff and Belcher.[10]
To a 250-mL Erlenmeyer flask containing a magnetic stir bar was added 2 mL of the commercial NaOCl solution, 100 mL of water, 1.5 mL of concd HCl , and 7 g of potassium iodide . The resulting dark brown solution was titrated with a 1 M solution of sodium thiosulfate ($Na_2S_2O_3$). The endpoint is reached when the solution becomes colorless. Using the following equations, the concentration of the NaOCl solution can be calculated. $OCl^- + 2I^- + 2H^+ \rightarrow H_2O + Cl^- + I_2$ $2S_2O_3 + I_2 \rightarrow S_4O_6 + 2I^-$
The solution (191 mL) used by the submitters was found to be 1.7 M in NaOCl and was then made 0.2 M in sodium hydroxide (NaOH) by the addition of 1.52 g of solid NaOH.
5. The epoxidation reaction is exothermic. The bleach is added over a period of 2-2.5 hr in order to maintain the desired temperature range. If the rate of addition appears to be faster, then the rate of stirring should be increased to ensure proper mixing of the biphasic mixture.
6. The physical properties are as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.95 (dd, 1 H, J = 2.9, 18.2), 3.19 (d, 1 H, J = 18.2), 4.10 (t, 1 H, J = 2.9), 4.25 (m, 1 H), 7.15-7.25 (m, 3 H), 7.48 (d, 1 H, J = 7.4) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.5, 57.5, 59.0, 125.0, 126.0, 126.1, 128.4, 140.8, 143.4 ; IR (NaCl): ν (cm^{-1}) 3045, 3029, 2913, 1474, 1466, 1419, 1372, 1230, 1175, 1000, 983 ; $[\alpha]^{23}_D$ +23.3° (hexanes, *c* 1.31); HRMS (CI, cool probe): calcd for $C_9H_{12}NO$ [M+NH_4] 150.0919, observed 150.0913 .
7. The enantiomeric excess of the epoxide is determined by HPLC analysis using a Chiracel OB column (25 cm × 4.6 mm, Daicel) eluted with EtOH/hexanes (5:95) at 1 mL/min, while monitoring at 254 nm. The retention times of the epoxide enantiomers are 11.1 (1S,2R) and 15.3 (1R,2S) min.
8. The submitters distilled the epoxyindane at lower pressure, bp 47-48°C (0.005 mm).
9. Solvents were freshly distilled from CaH_2 prior to reaction.
10. Fuming sulfuric acid was purchased from Aldrich Chemical Company, Inc. , and used as received. Approximately 10% of the acid is added before addition of the epoxide solution is begun.
11. The weight of the hydrolysis mixture is 225-250 g.
12. Slightly more or less NaOH solution may be required to reach the desired pH range.
13. The precipitation of the diastereomeric salt is rapid, and the solid may need to be broken up with a spatula in order to maintain proper mixing. Additional methanol may be added if needed.
14. The salt that precipitates initially is not diastereomerically pure, and the additional reflux period is necessary to allow equilibration to the diastereomerically pure material.
15. The salt is isolated as a methanol solvated complex, FW = 331.
16. The pH of the initial mixture is approximately 3.5. The free base begins to precipitate around pH 8.5.
17. The product is recrystallized from toluene in order to remove any of the trans isomer, as well as to dry the product. The hot mixture should be heated long enough to azeotropically remove water from the product.
18. The stereochemical purity of the product is determined by reacting a sample of the product (15 mg) with 2,4-dinitrofluorobenzene (13 μL) in CH_2Cl_2 (5 mL). The yellow solution is diluted with ethanol (1:10), then analyzed by HPLC on an N-naphthylleucine column (4.6 × 25 mm, Regis) eluted with IPA/hexanes (8:92) at 1 mL/min while monitoring at 350 nm. The retention times of the trans enantiomers are 17.4 and 19.1 min, while those of the cis enantiomers are 24.4 (1R,2S) and 27.1 (1S,2R) min. The product is enantio- and diastereomerically pure after recrystallization from toluene.
19. The physical properties are as follows: ^{1}H NMR (400 MHz, CD_3OD) δ: 2.88 (dd, 1 H, J = 2.9, 16.1), 3.05 (dd, 1 H, J = 5.4, 16.1), 4.13 (d, 1 H, J = 5.0), 4.39 (m, 1 H), 7.17-7.22 (m, 3 H), 7.38 (m, 1 H) ; ^{13}C NMR (100 MHz, CD_3OD) δ: 40.0, 60.4, 75.2, 125.3, 126.1, 127.8, 128.6, 141.8, 145.1 ; IR (NaCl): ν (cm^{-1}) 3343, 3290, 3170-3022, 2918, 1618, 1605, 1474, 1344, 1180, 1058 ; $[\alpha]^{23}_D$ −41.2° (MeOH, *c* 1.00, MeOH); HRMS (CI, cool probe): calcd for $C_9H_{12}NO$ [M+H] 150.0919, observed 150.0913 .

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The development of practical routes to the title compound has been the focus of intensive research effort since cis-aminoindanol was identified as a critical component of the highly effective HIV protease inhibitor indinavir (Crixivan®).[11,12] Reported routes include racemate synthesis followed by resolution via diastereomeric salts,[12] enzymatic resolution,[13 14] and asymmetric hydroxylation.[15] However, the use of a modified Ritter reaction to convert indene oxide to the corresponding cis-amino alcohol as described in this procedure constitutes the most direct and economical route devised thus far.[16 17] The application of the (salen)Mn-catalyzed epoxidation reaction[18 19 20 21 22] in the first step allows access to the requisite epoxide in good yield and good enantiomeric excess, thus rendering the overall process highly efficient. A final purification of the amino alcohol product involving formation of the L-tartrate salt serves to enhance both the chemical and stereochemical purity of the final product.

In addition to serving as a key stereochemical controlling element for synthesis of indinavir,[7,8,9] the title compound has proven to be a remarkably versatile chiral ligand and auxiliary for a range of asymmetric transformations including Diels-Alder reactions,[23 24 25 26 27] carbonyl reductions,[28 29 30] diethylzinc additions to aldehydes,[31] and enolate additions.[32 33 34 35 36]

References and Notes

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

(1S,2R)-1-Aminoindan-2-ol:
1H-Inden-2-ol, 1-amino-2,3-dihydro-, (1S-cis)- (12); (126456-43-7)

(1S,2R)-Indene oxide:
Indan, 1,2-epoxy- (8);
6H-Indeno[1,2-b]oxirene, 1a,6a-dihydro- (9); (768-22-9)

Indene (8);
1H-Indene (9); (95-13-6)

(R,R)-N,N'-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride:
Manganese, chloro[[2,2'-[1,2-cyclohexanediylbis(nitrilomethylidyne)]bis[4,6-bis(1,1-dimethylethyl) phenolato]](2-)-N,N',O,O']-, [SP-5-13-(1S-trans)]- (12); (135620-04-1)

4-Phenylpyridine N-oxide:
Pyridine, 4-phenyl-, 1-oxide (8,9); (1131-61-9)

Sodium hypochlorite solution:
Hypochlorous acid, sodium salt (8,9); (7681-52-9)

Acetonitrile TOXIC (8,9); (75-05-8)

Sulfuric acid, fuming:
Sulfuric acid, mixt. with
sulfur trioxide (9); (8014-95-7)

L-Tartaric acid:
Tartaric acid, L- (8);
Butanedioic acid, 2,3-dihydroxy-, [R-(R,R)]- (9); (87-69-4)