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of Reliable Methods
for the Preparation
of Organic Compounds

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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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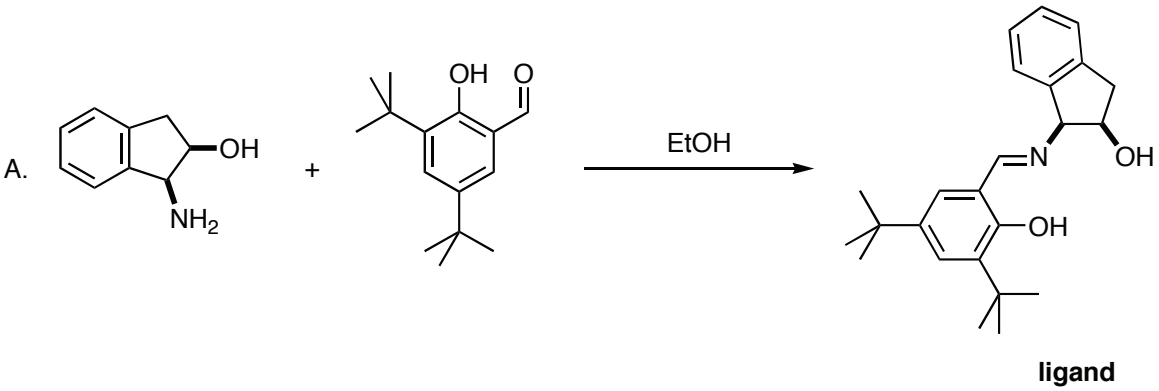
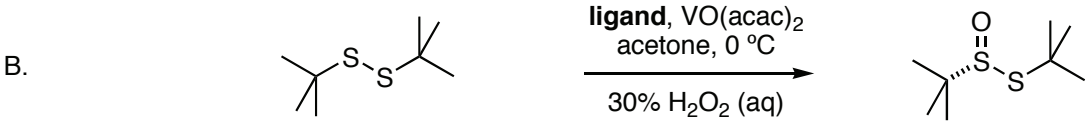
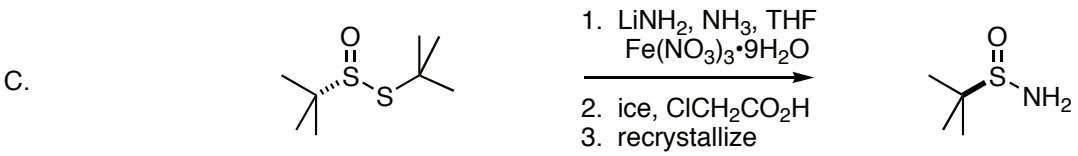
(R_S)-(+)-2-METHYL-2-PROPANESULFINAMIDE
[*tert*-Butanesulfinamide]







Submitted by Daniel J. Weix and Jonathan A. Ellman.[1]
Checked by Xiao Wang and Dennis P. Curran.

1. Procedures

A. (1S,2R)-1-[(2-Hydroxy-3,5-di-tert-butylbenzylidene)amino]indan-2-ol (Note 1). A 100-mL round-bottomed flask equipped with a magnetic stir bar is charged with (1*S*,2*R*)-(–)-*cis*-1-amino-2-indanol (0.77 g, 5.17 mmol) (Note 2), 3,5-di-*tert*-butyl salicylaldehyde (1.21 g, 5.16 mmol), and 33 mL of absolute ethanol. The yellow reaction mixture is stirred under argon for 2 h, and the solvent is removed under reduced pressure to give a yellow oil. The oil is dissolved in 33 mL of dichloromethane and the solvent

is again removed under reduced pressure. The dissolution and evaporation are repeated. After careful vacuum drying (the substance foams as the vacuum is initially applied), the resulting solid (1.85 g, 98%) is crushed to a yellow powder (Note 3) that is used without purification in Step B. *CAUTION: 30% hydrogen peroxide can cause burns.*

B. (R_S)-(+)-tert-Butyl tert-butanethiosulfinate. A three-neck 1-L round-bottomed flask fitted with an overhead stirrer and two rubber septa is charged with the ligand from *Step A* (1.85 g, 5.06 mmol) and vanadyl *bis*-acetylacetonate (1.33 g, 5.00 mmol) (Note 4). Acetone (250 mL) is added and the dark green reaction mixture is stirred vigorously for 30 min while open to the air. Di-*tert*-butyl disulfide (178 g, 1.00 mol) (Note 5) is slowly poured in from a graduated cylinder, and the resulting mixture is cooled to 0 ˚C (Note 6). The reaction mixture is stirred vigorously and 30% aq hydrogen peroxide (110 mL, 1.10 mol) (Notes 7 and 8) is added over 20 h by using two syringe pumps (Note 9). Upon the addition of the first few drops of hydrogen peroxide, the color of the mixture changes from dark green to purple, and the purple color deepens during the addition. Reaction progress can be monitored by ^{1}H NMR spectroscopy (Note 10). After 20 h, the reaction is quenched at 0 ˚C by adding 50 mL of saturated aqueous sodium thiosulfate by syringe pump over 30 min (Note 11). The purple color fades through red to light blue-green. The resulting mixture is transferred to a 2-L separatory funnel. The reaction flask is rinsed with hexanes (250 mL) and the hexanes wash is added to the separatory funnel. The mixture is shaken, the layers are separated and the aqueous layer is extracted with hexanes (2 x 250 mL). The combined organic layers are then washed with brine (50 mL), dried over sodium sulfate and filtered. The solvent is removed under reduced pressure at 30 ºC or lower. The resulting yellow or brown oil (216-231 g) (Notes 10 and 12) is used without purification for *part C* (Notes 13 and 14).

CAUTION: Ammonia is toxic and corrosive and should be used only in a well-ventilated fume hood.

CAUTION: This procedure generates hydrogen gas and should be performed in a well-ventilated fume hood.

CAUTION: tert-Butanethiol, although efficiently scavenged, is produced in stoichiometric quantities. It has a foul odor and is the odorant used for natural gas.

C. (R_S)-(+)-tert-Butanesulfinamide. A 5-L three-necked round-bottomed flask equipped with a mechanical stirrer (glass rod and glass paddle), a cold finger fitted with a gas inlet, and a Claisen adapter fitted with a glass stopper and a gas outlet connected to a mineral oil bubbler is placed under argon and cooled in a bucket of dry ice/acetone. The cold finger is filled with dry ice/acetone, and the gas inlet is changed from argon to an ammonia cylinder (Note 15). The ammonia gas pressure is adjusted so that most of the ammonia is condensed into the vessel as it passes through the cold finger (Note 16). After about 2 L of ammonia is condensed (about 2.5 h), the mineral oil bubbler is removed from the Claisen adapter gas outlet and replaced with an argon line. The ammonia line is removed from the cold finger gas inlet and replaced with a mineral oil bubbler.

The reaction mixture at –75˚C (internal temperature) is flushed gently with an argon stream, and $Fe(NO_3)_3 \bullet 9H_2O$ (1.0 g, 2.48 mmol) (Note 17) is added. The mixture turns brown as dissolution occurs on stirring. The Claisen adaptor is replaced with an adaptor containing a low temperature thermometer. The cooling bath is lowered and pieces of lithium ribbon (17.4 g, 2.50 mol) (Note 18) are added with tweezers in ~1 g portions (Note 19). Each piece is cut in half just prior to addition to ensure fast dissolution and reaction. As each piece of lithium is added, the mixture briefly turns a dark blue color. This fades to give a grey suspension of lithium amide with concomitant evolution of hydrogen gas (Note 19). Once the reaction returns to the grey color, another piece of lithium is added. The dry ice/acetone bath is periodically raised to contact the bottom of the flask to slow the refluxing caused by the formation of $LiNH_2$ (Note 19). After the addition of the lithium is complete (about 1.5 h), the reaction mixture is allowed to reflux for 15 minutes (Note 20), and then submerged in the dry ice/acetone bath.

After cooling to –78 ˚C (about 30 minutes) and replacement of the thermometer adaptor by an addition funnel, a solution of crude (R_S)-(+)-*tert*-butyl *tert*-butanethiosulfinate (entire crude product from Step B, 1.00 mol) in 320 mL of freshly distilled, dry THF is added to the vigorously stirring reaction mixture over 45 minutes via the addition funnel (Note 21). The addition funnel is rinsed with a small amount (5-10 mL) of THF and this is added to the reaction mixture. The addition funnel is replaced by the thermometer adaptor. After one hour at –78 to –72 ºC, the cooling bath is removed, stirring is slowed to the lowest possible rate and the reaction

mixture is allowed to slowly warm to room temperature overnight (15 h) under a stream of argon (Note 22).

The resulting thick gray mixture, still under an argon stream, is cooled in an ice-water bath. Ice (540 g, 30 mmol) is added in one portion, and the dark green mixture is stirred until it is mostly homogeneous (Note 23). Chloroacetic acid (104 g, 1.10 mol) (Note 24) is added to the ice-cold mixture in five portions over 20 minutes. The resulting mixture is stirred overnight (12 h) at ambient temperature under argon. The claret solution is poured into a 2 L separatory funnel and extracted with methylene chloride (6 x 1 L). The combined organic layers are dried over Na_2SO_4, and filtered through a pad of celite. The solvent is removed under reduced pressure. Hexanes (200 mL) are added and the solvent is removed under reduced pressure. More hexanes (50 mL) are added and the evaporation is repeated. The resulting yellow-orange solid is triturated (Note 25) with hexanes (250 mL) in a 500 mL Erlenmeyer flask. After the solids are crushed, a magnetic stir bar is added and the slurry is stirred for 30 minutes. The solids are collected on a suction filter, washed with hexanes (15 mL), and suction-dried (Note 26). The triturated material is then recrystallized by dissolving it in boiling hexanes (150 mL), followed by slow cooling to room temperature with fast stirring. The crystals are collected by suction filtration and washed with cold hexanes (300 mL, precooled to –30 ˚C) and suction-dried to provide 84.9-86.9 g (70-72% from di-*tert*-butyl disulfide) of the desired product (Note 27).

2. Notes

1. This ligand has been reported several times.[2] This procedure is adapted from the procedure of Ruck and Jacobsen.[2d] (1*S*,2*R*)-(–)-*cis*-1-Amino-2-indanol leads to (R_S)-*tert*-butanesulfinamide while (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol leads to (S_S)-*tert*-butanesulfinamide.

2. (1*S*,2*R*)-(–)-*cis*-1-Amino-2-indanol was purchased from Strem (submitters) or Aldrich (checkers). 3,5-Di-*tert*-butyl-2-hydroxy-benz-aldehyde was purchased from Aldrich.

3. The yellow powder exhibited the following features: mp 64 - 68 ºC (65 - 68 ˚C lit.[2c]); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.33 (s, 9 H), 1.43 (s, 9 H), 2.17 (br s, 1 H), 3.13 (dd, J = 4.9, 15.9 Hz, 1 H), 3.26 (dd, J = 5.8, 15.9 Hz, 1 H), 4.69 (m, 1 H), 4.81 (d, J = 5.3 Hz, 1 H), 7.19 (d, J = 2.2 Hz, 1 H),

7.20-7.32 (m, 4 H), 7.44 (d, J = 2.3 Hz, 1 H), 8.63 (s, 1 H), 13.12 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.4, 31.5, 34.1, 35.0, 39.7, 75.2, 75.7, 117.8, 124.9, 125.4, 126.5, 127.0, 127.6, 128.5, 136.9, 140.4, 140.8, 140.9, 157.9, 168.3; IR (neat) 739, 755, 1626, 2957 cm^{-1}; HRMS-FAB (*m/z*) calcd for $C_{24}H_{31}NO_2$, 365.2355, found, 365.2353. Anal. Calcd for $C_{24}H_{31}NO_2$: C, 78.86; H, 8.55; N, 3.83. Found: C, 79.15; H, 8.69; N, 3.69.

4. Vanadium (IV) bis(acetylacetonato)oxide was purchased from Strem (submitters) or Aldrich (checkers). Industrial Grade acetone was used as received.

5. Di-*tert*-butyl disulfide was purchased from Acros and distilled (91-96 ºC/10 mmHg). The distillation proceeds smoothly if the pot is not allowed to boil vigorously, otherwise excessive foaming and bumping can result. Avoid Boileezers® or stir bars in the pot.

6. A recirculating chiller (Lauda RM-6B or FTS System) with an external cooling coil and a 2-propanol bath was used. Slightly higher temperatures result in a small decrease in enantioselectivity, but no decrease in conversion.

7. Hydrogen peroxide (30% aq, stabilized with sodium stannate) was purchased from Fisher Scientific.

8. This mixture of hydrogen peroxide, acetone, and water is considered safe. See the "hydrogen peroxide product information manual" available from Eka chemicals (www.eka.com).

9. The submitters used a model NE-1600 programmable six-syringe pump from New Era Pump Systems, Inc., while checkers used a two separate syringe pumps model M361 from Thermo Orion.

10. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.39 (s, 9 H), 1.54 (s, 9 H). When a reaction is incomplete, a starting material resonance, is visible at 1.31 ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.2, 32.3, 48.6, 59.3. Analysis by chiral phase HPLC (Daicel Chiralpak AS-H column, 25 cm x 0.46 cm; 97:3 hexanes:2-propanol; 1 mL/min; 254 nm; (*S*) r_t = 6.6 min; (*R*) r_t = 7.8 min) shows that the product has an 86-87% ee.

11. It is best to quench any remaining hydrogen peroxide before allowing the reaction to warm to room temperature because a mild exotherm can occur due to hydrogen peroxide decomposition upon warming. When saturated aq sodium thiosulfate was added in one portion with cooling, an

exotherm occurred which raised the internal temperature of the reaction to 32 ºC; therefore, slow addition with adequate cooling is preferred.

12. By ^{1}H NMR spectroscopic analysis, the product contained less than 1% acetone (peak at 2.17 ppm in $CDCl_3$). If acetone is still present, it is removed by adding more hexanes and removing the azeotrope under reduced pressure. The checkers sometimes observed small amounts of an insoluble yellow solid in the late stages of solvent removal. This is elemental sulfur (mp 111-113 ºC, lit. 112.8 ºC), and was removed by decantation. The decomposition of $S_2O_3^{-2}$ to S and SO_3^{-2} is a well-known reaction.

13. *tert*-Butyl *tert*-butanethiosulfinate is a useful starting material for the synthesis of *tert*-butyl sulfoxides. It can be purified by distillation or crystallization if needed.[2a]

14. The thiosulfinate should be stored at –20 ºC. At this temperature it is a solid and no decomposition has been observed over several months. Gradual decomposition and erosion of enantiopurity occur on storage at room temperature.

15. Ammonia gas (99.99% pure) was purchased from Matheson or Praxair.

16. The dry ice evaporates rapidly from the cold finger if the ammonia is passed in too quickly.

17. $Fe(NO_3)_3 \bullet 9H_2O$ was purchased from Mallinckrodt (submitters) or Aldrich (checkers).

18. The submitters used lithium bars (12.7 mm x 165 mm, 99.9 % pure) purchased from Alfa Aesar. The checkers used lithium ribbon (dissolves more rapidly) purchased from Aldrich (45 mm x 0.75 mm, 99.9%). The lithium was washed with hexanes to remove storage oil prior to rapid weighing in a tared beaker of hexanes. The thermometer adaptor was partially removed to drop in the lithium.

19. Lithium amide does not form rapidly at –78 ºC, but the blue color begins to form as the mixture is warmed to about –45 ˚C. During the addition, the cooling bath is raised and lowered periodically to keep the internal temperature between –50 ˚C and –45 ˚C.

20. All the lithium must be dissolved and converted to lithium amide to prevent an exotherm from occurring during the subsequent evaporation of the ammonia.

21. The internal temperature is kept at –73 ˚C or below. The thiosulfinate is added directly into the reaction mixture to prevent it from

solidifying on the sidewalls of the vessel. Adjusting the mixing speed to wash any solidified material back into the reaction mixture may be necessary.

22. The submitters report that stirring is not needed during this stage.

23. The initially thick precipitate largely dissolves, but a small amount of powder remains suspended. If the mixture is not stirred during the ammonia evaporation or if the stirring stops, it can be difficult to restart the stirrer. Churning the glass rod by hand breaks up the mass so that stirring can be reinitiated.

24. Chloroacetic acid was purchased from Acros or Aldrich.

25. Trituration improves the enantiopurity and removes most of the colored impurities. The recovery in the trituration will decrease if any CH_2Cl_2 remains in the crude material because *tert*-butanesulfinamide is very soluble in this solvent.

26. This material has a 95% ee and represents a 75% yield from di-*tert*-butyl disulfide.

27. The product is a white to off-white crystalline solid; mp 102 - 105 ºC (102 - 103 ºC lit.[2a]); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.22 (s, 9 H), 3.73 (s, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.1, 55.2; IR (neat) 1030, 1363, 1460, 1588, 3119, 3216 cm^{-1}; Anal. Calcd for $C_4H_{11}NOS$: C, 39.64; H, 9.15; N, 11.56. Found: C, 39.62; H, 9.12; N, 11.29. Chiral phase HPLC (Daicel Chiralpak AS-H column, 25 cm x 0.46 cm; 90:10 hexanes:ethanol; 1.2 mL/min; 220 nm; (*R*) r_t = 7.9 min; (*S*) r_t = 10.6 min) shows that the product has ≥ 99% ee; The submitters report that the analysis can also be conducted on a Daicel Chiralpak OD column; 93/7, hexanes:i-PrOH, 1 mL/min, 220 nm; (S) r_t = 23.7 min, (R) r_t = 27.7 min;

Waste Disposal Information

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

3. Discussion

Chiral amines are key components of many pharmaceutical agents, materials, and catalysts. Since its introduction in 1997,[3] enantiopure *tert*-

butanesulfinamide has proven to be an extremely versatile chiral ammonia equivalent for the asymmetric synthesis of amines.[4]

The original synthesis included an oxidation that did not scale well and did not provide procedures for removing the offensive *tert*-butane thiol odor. Recent work has improved the scalability of the oxidation, allowed easy access to both (R_S)- and (S_S)-*tert*-butanesulfinamide, and eliminated the tedious distillation of the *tert*-butyl *tert*-butanethiosulfinate intermediate.[2g] This procedure used sodium hydroxide solutions to trap the thiol; however, the thiol removal was incomplete. *tert*-Butane thiol is the primary odorant added to natural gas because its odor can be detected at very low levels, and because it is heavier than air and resists oxidation well.

We initially explored trapping the thiol by the use of gas washing bottles filled with bleach solution. While this was effective at controlling odor, it presents an unnecessary danger when combined with ammonia (possible formation of chlorine gas, nitrogen trichloride, or hydrazine; explosion hazard). After a survey of various methods, we found that evaporation of the ammonia before quenching the reaction with ice eliminated thiol odor during the ammonia removal process. Furthermore, if chloroacetic acid is then added to the crude aqueous solution and the mixture stirred, the residual lithium *tert*-butanethiolate reacts with the lithium chloroacetate to form the highly water soluble lithium (*tert*-butylthio)acetate. At this stage, the reaction mixture has no discernible thiol odor. Simple extraction with methylene chloride then separates the sulfinamide from the lithium (*tert*-butylthio)acetate. Trituration followed by crystallization yields highly enantioenriched *tert*-butanesulfinamide. This procedure allows for the preparation of either enantiomer of *tert*-butanesulfinamide in good yield on mole scale with no thiol odor and only trituration and crystallization for purification.

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Appendix
Chemical Abstracts Nomenclature (Registry Number)

(1*S*,2*R*)-(–)-*cis*-1-Amino-2-indanol: 1H-Inden-2-ol, 1-amino-2,3-dihydro-, (1S,2R)-; (126456-43-7)

3,5-Di-*tert*-butyl salicylaldehyde: Benzaldehyde, 3,5-bis(1,1-dimethylethyl)-2-hydroxy-; (37942-07-7)

(1*S*,2*R*)-1-[(2-Hydroxy-3,5-di-*tert*-butylbenzylidene)amino]indan-2-ol: 1H-Inden-2-ol, 1-[[[3,5-bis(1,1-dimethylethyl)-2-hydroxyphenyl]methylene]amino]-2,3-dihydro-, (1S,2R)-; (212378-89-7)

(R_S)-(+)-*tert*-Butyl *tert*-butanethiosulfinate: 2-Propanesulfinothioic acid, 2-methyl-, S-(1,1-dimethylethyl) ester, [S(R)]-; (67734-35-4)

Vanadyl *bis*-acetylacetonate: Vanadium, oxobis(2,4-pentanedionato-**k**O,**k**O')-; (3153-26-2)

Di-*tert*-butyl disulfide: Disulfide, bis(1,1-dimethylethyl); (110-06-5)

Hydrogen peroxide; (7722-84-1)

Sodium thiosulfate: Thiosulfuric acid, disodium salt; (7772-98-7)

$Fe(NO_3)_3 \bullet 9H_2O$ (Iron(III) nitrate nonahydrate): Nitric acid, iron(3+) salt, nonahydrate; (7782-61-8)

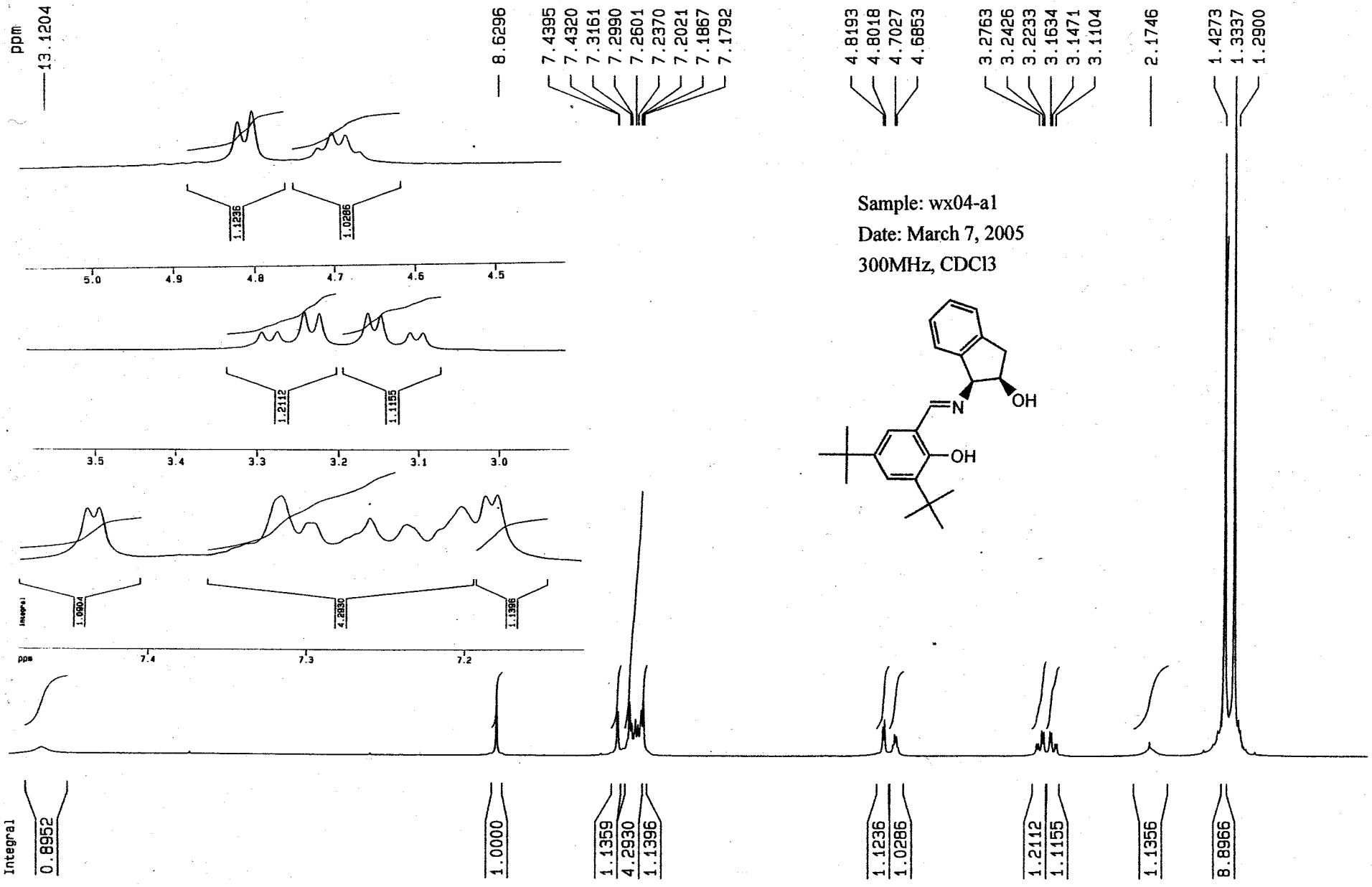
Lithium; (7439-93-2)

Chloroacetic acid; (79-11-8)

(R_S)-(+)-2-Methyl-2-Propanesulfinamide [*Tert*-Butanesulfinamide]: 2-Propanesulfinamide, 2-Methyl-, [S(R)]-; (196929-78-9)

wx0307-1

wx04-A1 The ligand (in CDCl3) for coupling constants



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1.54393
1.53775
1.47332
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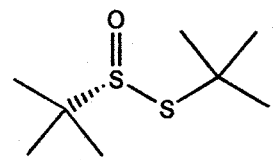
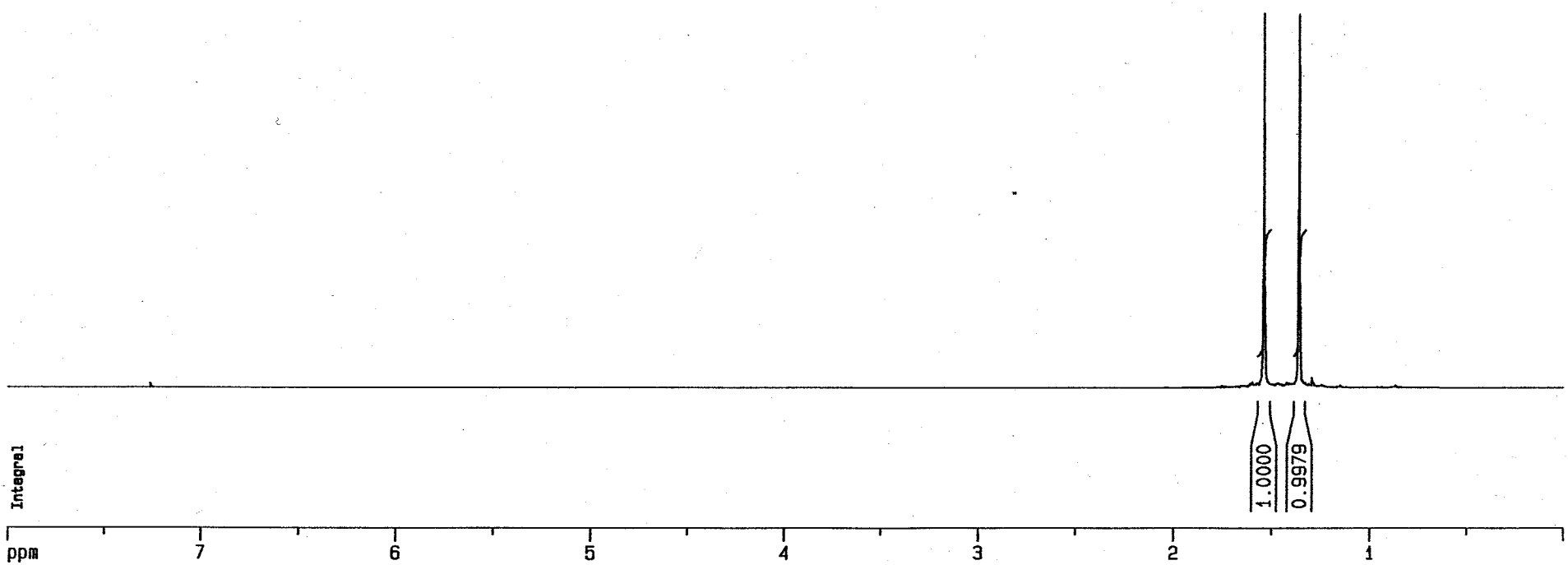
Sample: wx04-b3
Date: Jan 23, 2005
300MHz, CDCl3





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sulfinamide C-1