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for the Preparation
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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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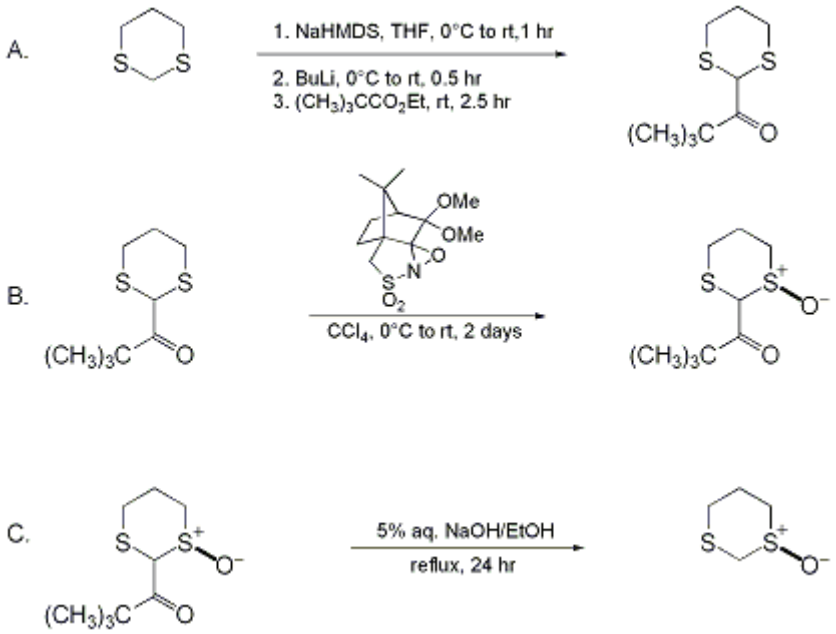
1S-(−)-1,3-DITHIANE 1-OXIDE

[1,3-Dithiane, 1-oxide, (S)-]



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1. Procedure

A. 2-(2,2-Dimethylpropanoyl)-1,3-dithiane . To 43.0 g (0.358 mol) of 1,3-dithiane (Note 1) at 0°C under a nitrogen atmosphere is added 396 mL of a 1 M solution of sodium hexamethyldisilazide in tetrahydrofuran (THF) (Note 2) and (Note 3). The resulting yellow solution is allowed to reach room temperature and then stirred at room temperature for 1 hr. The solution is cooled to 0°C, and 172 mL of a 2.5 M solution of butyllithium in hexanes (Note 4) is added. The reaction mixture is allowed to warm to room temperature and then stirred at room temperature for 30 min. Ethyl 2,2-dimethylpropanoate (65.0 mL, 0.427 mol) (Note 5) is added, and the mixture is stirred at room temperature for 2.5 hr. An aqueous saturated solution of ammonium chloride (200 mL) is added, and the aqueous phase is extracted three times with 200 mL of dichloromethane (Note 6). The combined organic extracts are washed with 100 mL of water and dried over anhydrous magnesium sulfate . The solvents are removed under reduced pressure to give a yellow solid. Repeated trituration with petroleum ether 40-60°C (Note 7) followed by filtration gives 51.0-55.1 g (70-75%) of 2-(2,2-dimethylpropanoyl)-1,3-dithiane as colorless needles, mp 97-99°C (Note 8).

B. anti- and syn-1S-(2,2-Dimethylpropanoyl)-1,3-dithiane 1-oxide . (+)-[(8,8-Dimethoxycamphoryl) sulfonyl]oxaziridine (51.0 g, 0.176 mol) (Note 9) is added to a cooled, stirred solution of 36.0 g (0.176 mol) of 2-(2,2-dimethylpropanoyl)-1,3-dithiane in 1000 mL of carbon tetrachloride (Note 10) at 0°C. The reaction mixture is allowed to reach room temperature, and stirring is continued at room temperature for a further 48 hr. The reaction mixture is filtered to remove the bulk of the (+)-[(8,8-dimethoxycamphoryl)sulfonyl]imine, and the filtrate is evaporated to dryness under reduced pressure. The residue is purified by passage through a short column of silica gel using dichloromethane as initial eluant to remove residual (+)-[(8,8-dimethoxycamphoryl)sulfonyl]imine. The column is then flushed with ethyl acetate to give 29.8-33.5 g (77-86%) of an ca. 3:1 mixture of anti- and syn-1S-(2,2-dimethylpropanoyl)-1,3-dithiane 1-oxide as a colorless crystalline solid, mp 103-105°C (Note 11).

C. (1S)-(−)-1,3-Dithiane 1-oxide . A mixture of anti- and syn-1S-2-(2,2-dimethylpropanoyl)-1,3-dithiane 1-oxide (33 g, 0.150 mol) is dissolved in 500 mL of ethanol (Note 12), and 200 mL of aqueous 5% sodium hydroxide is added. The mixture is heated under reflux for 24 hr. The mixture is allowed to cool, and 500 mL of dichloromethane is added. The organic layer is separated, and the aqueous phase is extracted four times, with 100 mL of dichloromethane . The combined organic extracts are dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure to give a beige solid. The solid is triturated with diethyl ether to give 13 g (64%) of 1S-(−)-1,3-dithiane 1-oxide as a colorless solid, mp 90-92°C (Note 13) and (Note 14).

2. Notes

1. 1,3-Dithiane was stored in a desiccator over self-indicating silica gel.
2. Tetrahydrofuran was distilled under nitrogen from the benzophenone ketyl radical.
3. Sodium hexamethyldisilazide [sodium bis(trimethylsilyl)amide] was purchased from the Aldrich Chemical Company, Inc., in 100- or 800-mL bottles as a 1 M solution in tetrahydrofuran. Glassware used for moisture sensitive reactions was dried at 180°C and allowed to cool in a desiccator over self-indicating silica gel. Reactions were carried out under a slight positive static pressure of argon.
4. Butyllithium was purchased from the Aldrich Chemical Company, Inc. , in 800-mL bottles as a 2.5 M solution in hexanes; the molarity was determined by titration against a solution of diphenylacetic acid.
5. Commercially available reagents were used as supplied unless otherwise stated.
6. Dichloromethane was dried by distillation from calcium hydride .
7. Petroleum ether (40-60°C) was distilled prior to use.
8. The analytical data for 2-(2,2-dimethylpropanoyl)-1,3-dithiane are as follows: Found: C, 52.73; H, 7.87. $C_9H_{16}OS_2$ requires C, 52.90; H, 7.89%; IR (Nujol) cm^{-1}: 2900, 1673 ; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.24 (s, 9 H), 1.95-2.09 (m, 1 H), 2.13-2.23 (m, 1 H), 2.56 (ddd, 2 H, J = 2.4, 7.0, 12.5), 3.43 (dt, 2 H, J = 2.4, 12.5), 4.51 (s, 1 H) ; m/z (El) 204.06445 (M^+); $C_9H_{16}OS_2$ requires 204.06425 .
9. For the preparation of (+)-[(8,8-dimethoxycamphoryl)sulfonyl]oxaziridine see: Chen, B.-C.; Murphy, C. K.; Kumar, A.; Reddy, R. T.; Clark, C.; Zhou, P.; Lewis, B. M.; Gala, D.; Mergelsberg, I.; Scherer, D.; Buckley, J.; DiBenedetto, D.; Davis, F. A. *Org. Synth., Coll. Vol. IX* **1998**, 212. A somewhat modified procedure[3] is as follows: *(+)-[(8,8-Dimethoxycamphoryl)sulfonyl]oxaziridine* . Aliquat 336® (tri-n-octyl-methylammonium chloride) (5.0 mL, 10.9 mmol) is added to a stirred solution of 50.0 g (183 mmol) of (+)-[(8,8-dimethoxycamphoryl)sulfonyl]imine in 250 mL of dichloromethane at 0°C. A solution of 50.0 g (362 mmol) of potassium carbonate in 100 mL water is added and the biphasic reaction mixture is stirred for 5 min. A commercial solution (30% w/v) of hydrogen peroxide (83.0 mL, 732 mmol) is added dropwise over 30 min. The reaction is then allowed to warm to room temperature and stirred for about 6-7 hr (Note 15). The organic layer is separated and the aqueous phase extracted three times, each with 100 mL of dichloromethane . Residual hydrogen peroxide in the aqueous phase is carefully destroyed by the addition of saturated aqueous sodium sulfite . The combined organic extracts are rapidly washed with an aqueous solution of 5.0 g of sodium sulfite in 100 mL water and 100 mL of saturated brine and dried over anhydrous magnesium sulfate . Removal of the solvent under reduced pressure, at a bath temperature not exceeding 40°C, gives a white solid consisting of (+)-[(8,8-dimethoxycamphoryl)sulfonyl]oxaziridine contaminated with (+)-[(8,8-dimethoxycamphoryl)sulfonyl] imine. Recrystallization from absolute ethanol furnishes 51.3 g (97%) of (+)-[(8,8-dimethoxycamphoryl)sulfonyl]oxaziridine, mp 188-190°C (Note 16).
10. Carbon tetrachloride was used as supplied without further purification.
11. The analytical data for anti- and syn-1S-(2,2-dimethylpropanoyl)-1,3-dithiane 1-oxides are as follows: Found: C, 48.91; H, 7.35. $C_9H_{16}O_2S_2$ requires C, 49.06; H, 7.32; IR (Nujol) cm^{-1}: 2900, 1706, 1030 ; ^1H NMR (400 MHz, $CDCl_3$) δ for anti-: 1.26 (s, 9 H), 2.04-2.15 (m, 1 H), 2.45-2.70 (m, 2 H), 2.75-2.90 (m, 2 H), 3.44-3.56 (m, 1 H), 4.72 (s, 1 H); for syn-: 1.24 (s, 9 H), 2.22-2.35 (m, 1 H), 2.45-2.55 (m, 2 H), 3.00-3.15 (m, 2 H), 3.97 (dt, 1 H, J = 3.5, 13.8), 4.98 (s, 1 H) ; m/z (EI) 220.05931 (M^+); $C_9H_{16}OS_2$ requires 220.059187 ; ee (anti) = 87%, ee (syn) = 88% from ^1H NMR studies (Note 17).
12. Ethanol was used as supplied without further purification.
13. The analytical data for 1S-(−)-1,3-dithiane 1-oxide are as follows: Found: C, 35.18; H, 5.93. $C_4H_8OS_2$ requires C, 35.27; H, 5.89; IR (Nujol) cm^{-1}: 2927, 1047 ; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.10-2.35 (m, 1 H), 2.45-2.77 (m, 4 H), 3.35 (ddd, 1 H, J = 3.0, 6.0, 9.5), 3.66 (d, 1 H, J = 12.7), 4.03 (d, 1 H, J = 12.7) ; m/z (EI) 136.00151 (M^+); $C_4H_8OS_2$ requires 136.00166 ; ee = 87% from ^1H NMR studies (Note 17).

14. The checkers obtained the product in about 54% yield and found flash chromatography to be more effective in its purification. This was accomplished using a 16-cm × 5-cm column of silica gel and $CHCl_3$/MeOH (96:4) as the eluant. With collection of ca. 50-mL fractions, the product was observed in fractions 12-21. Visualization of the product was accomplished by TLC (product R_f = 0.4 in $CHCl_3$/MeOH 96:4, anisaldehyde stain).
15. The checkers noted that complete oxidation typically required ca. 6-7 hr and recommend checking the progress of the reaction in the following way: a 1-mL aliquot is removed from the organic layer, diluted with 2 mL of methylene chloride, and analyzed by TLC eluting with methylene chloride (I_2 visualization); imine R_f = 0.34, oxaziridine R_f = 0.51
16. The analytical data for (+)-[(8,8-dimethoxycamphoryl)sulfonyl]oxaziridine are as follows: Found: C, 49.77; H, 6.62; N, 4.88. $C_{12}H_{19}NO_5S$ requires C, 49.83; H, 6.57; N, 4.84; IR (CH_2Cl_2 film) cm^{-1}: 1367, 1345, 1165 ; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.06 (s, 3 H), 1.32 (s, 3 H), 1.75-2.30 (m, 5 H), 3.08 (d, 1 H, J = 12.0), 3.29 (d, 1 H, J = 12.0), 3.27 (s, 3 H), 3.34 (s, 3 H, CH_3) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.5, 21.6, 28.1, 29.3, 45.1, 47.4, 52.9, 50.5, 50.8, 54.6, 97.6, 102.8 ; m/z (CI) 290.10619 (MH^+); $C_{12}H_{20}NO_5S$ requires 290.10622 ; $[\alpha]^{20}_D$ +91° ($CHCl_3$, *c* 3.00) (Note 17).
17. Optical rotations were measured on Optical Activity AA-1000 or polAAr 2001 polarimeters operating at 589 nm, corresponding to the sodium D line. Enantiomeric excesses were determined by ^1H NMR chiral shift reagent studies using 10 equiv of (R)-(−)- or (S)-(+)-2,2,2-trifluoro-1-(9-anthryl) ethanol (Pirkle reagent).

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

Non-racemic chiral sulfoxides have become important as sources of chirality for asymmetric carbon-carbon bond formation.[4] For example, we have developed 1,3-dithiane 1-oxide (DiTOX) units as effective moieties for stereocontrol of a range of carbonyl group reactions, including enolate alkylation and amination, Mannich reaction, reduction, and heterocycloaddition.[5] While we have been able to prepare several 2-monosubstituted[6] and 2,2-disubstituted-1,3-dithiane 1-oxides[7] in high enantiomeric excesses (ee) on scales of a few grams, we had difficulty until recently in preparing the parent compound, 1,3-dithiane 1-oxide, with very high ee in quantities of more than ca. 5 g.[8] Enantiomerically pure 1,3-dithiane 1-oxide has previously been prepared via adducts with (+)-camphor,[9] and, by ourselves, using modified Sharpless oxidation techniques.[8,10,11]

We have recently reported that [(8,8-dimethoxycamphoryl)sulfonyl]oxaziridine is a particularly effective reagent for asymmetric sulfide oxidation, especially in non-aryl sulfide substrates.[3] Here we report a three-step chemical synthesis of 1,3-dithiane 1-oxide with very high ee that is based upon such an oxidation as the key step. The procedure is effective for production of multigram quantities of material of either absolute configuration. The sequence is illustrated for the preparation of 1S-(−)-1,3-dithiane 1-oxide.

The route is based upon an acylation-oxidation-deacylation sequence, with commercially available, inexpensive 1,3-dithiane employed as the starting material. 2-Acyl-1,3-dithianes have proved to be particularly effective substrates for asymmetric oxidation in our hands,[8,10,3,12] and as 2-(2,2-dimethylpropanoyl)-1,3-dithiane undergoes this asymmetric oxidation most efficiently (ca. 90% ee), it was chosen as the intermediate.

References and Notes

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

1S-(−)-1,3-Dithiane 1-oxide:
1,3-Dithiane, 1-oxide, (S)- (10); (63865-78-1)

2-(2,2-Dimethylpropanoyl)-1,3-dithiane:
1-Propanone, 1-(1,3-dithian-2-yl)-2,2-dimethyl- (10); (73119-31-0)

1,3-Dithiane:
m-Dithiane (8);
1,3-Dithiane (9); (505-23-7)

Sodium hexamethyldisilazide (NHMDS): Aldrich:
Sodium bis(trimethylsilyl)amide:
Disilazane, 1,1,1,3,3,3-hexamethyl-, sodium salt (8);
Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, sodium salt (9); (1070-89-9)

Butyllithium:
Lithium, butyl- (8,9); (109-72-8)

Ethyl 2,2-dimethylpropanoate: Aldrich: See:
Ethyl trimethylacetate:

Propanoic acid, 2,2-dimethyl-, ethyl ester (9); (3938-95-2)

anti-1S-(2,2-Dimethylpropanoyl)-1,3-dithiane 1-oxide:
1-Propanone, 2,2-dimethyl-1-(1-oxido-1,3-dithian-2-yl)-, (1S-trans)- (13); (160496-17-3)

(+)-[(8,8-Dimethoxycamphoryl)sulfonyl]oxaziridine:
4H-4a,7-Methanooxazirino[3,2-i][2,1]benzisothiazole, tetrahydro-8,8-dimethoxy-9,9-dimethyl-, 3,3-dioxide, [2R-(2α,4aα,7α, 8aR)]- (12); (131863-82-6)

Aliquat 336: Methyltri-n-octylammonium chloride:
Ammonium, methyltrioctyl-, chloride (8);
1-Octanaminium, N-methyl-N,N-dioctyl-, chloride (9); (5137-55-3)

Hydrogen peroxide (8,9); (7722-84-1)