



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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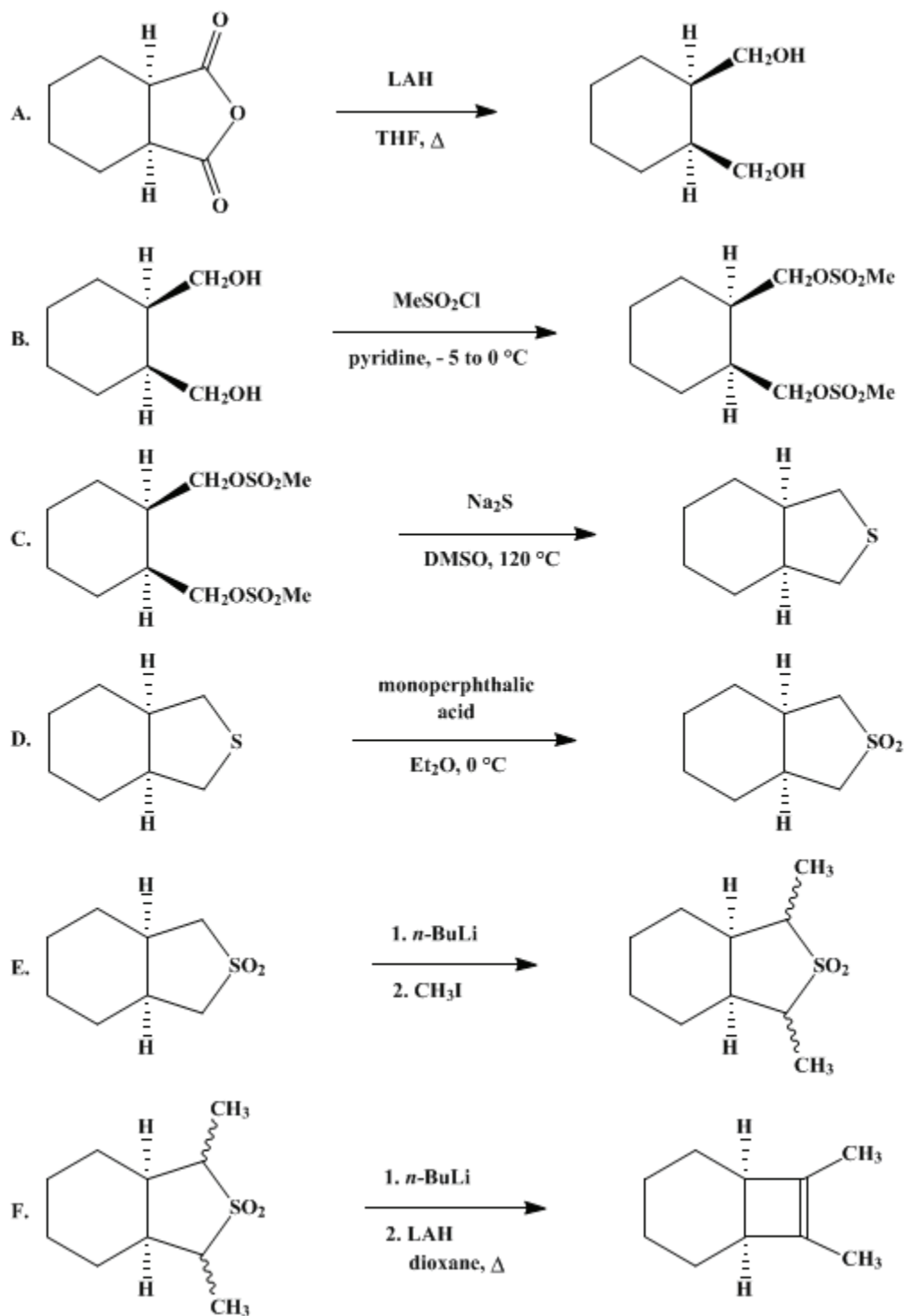
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 6, p.482 (1988); Vol. 57, p.53 (1977).

1,2-DIMETHYLCYCLOBUTENES BY REDUCTIVE RING-CONTRACTION OF SULFOLANES: *cis*-7,8-DIMETHYLBICYCLO[4.2.0]OCT-7-ENE

[Bicyclo[4.2.0]oct-7-ene, 7,8-dimethyl-, *cis*-]



Submitted by James M. Photis and Leo A. Paquette¹.

1. Procedure

Caution! Steps B and C should be performed in a hood because of the noxious odors produced.

Methyl iodide, in high concentrations for short periods or in low concentrations for long periods, can cause serious toxic effects in the central nervous system. Accordingly, the American Conference of Governmental Industrial Hygienists² has set 5 p.p.m., a level which cannot be detected by smell, as the highest average concentration in air to which workers should be exposed for long periods. The preparation and use of methyl iodide should always be performed in a well-ventilated fume hood. Since the liquid can be absorbed through the skin, care should be taken to prevent contact.

A. *cis*-1,2-Cyclohexanedimethanol. A 3-l., three-necked, round-bottomed flask fitted with a mechanical stirrer, addition funnel, and condenser is charged with 1.5 l. of anhydrous tetrahydrofuran (Note 1). With vigorous stirring, 14.8 g. (0.389 mole) of lithium aluminum hydride is added, followed by a solution of 50.0 g. (0.325 mole) of *cis*-1,2-cyclohexanedicarboxylic anhydride in 300 ml. of tetrahydrofuran introduced in a thin stream over 30 minutes. The resulting suspension is maintained at the reflux temperature for 3 hours with a heating mantle, after which heating is ceased and 100 ml. of a freshly prepared (Note 2), saturated aqueous sodium sulfate is cautiously added dropwise (Note 3). Highly granular insoluble salts, which change in appearance from gray to white, are removed by suction filtration through a Büchner funnel and washed thoroughly with diethyl ether. The combined filtrates are freed of solvent on a rotary evaporator, yielding 46.0–46.5 g. (98–100%) of the diol as a colorless, viscous oil which may slowly crystallize, m.p. 38–40° (Note 4). Pure *cis*-1,2-cyclohexanedimethanol is reported to have m.p. 42–43°. ^{3,4,5}

B. *cis*-1,2-Cyclohexanedimethanol dimethanesulfonate. A 5-l., three-necked, round-bottomed flask, immersed in an ice-salt bath and fitted with a mechanical stirrer and an addition funnel, is charged with a solution of 111 g. (0.969 mole) of methanesulfonyl chloride in 1.2 l. of pyridine. While cooling and stirring, a solution of 46.4 g. (0.322 mole) of *cis*-1,2-cyclohexanedimethanol in 250 ml. of pyridine is added dropwise at a rate such that the temperature does not exceed 0° (Note 5). Upon completion of the addition, the mixture is stirred at –5° to 0° for an additional 2 hours. Two liters of cold, 10% hydrochloric acid is introduced at a rate which maintains the reaction mixture below 20° (Note 5). The solid which separates is isolated by suction filtration, washed sequentially with 1 l. of dilute hydrochloric acid and 2 l. of water, and air-dried, yielding 93–95 g. (96–98%) of the dimethanesulfonate, m.p. 66–67.5°. Recrystallization from methanol gives needles melting at 75–76° (Note 6).

C. *cis*-8-Thiabicyclo[4.3.0]nonane. A 3-l., three-necked, round-bottomed flask fitted with a mechanical stirrer, capillary tube, heating mantle, and 90° adapter connected to a condenser and receiving flask is charged with 240 g. (1.00 mole) of recrystallized sodium sulfide nonahydrate (Note 7) and 2 l. of dimethyl sulfoxide. As the mixture is stirred, the internal pressure is reduced to 30 mm., and heat is applied until 300–350 ml. of distillate is collected (Note 8). After cooling to 40°, the capillary and take-off adapter are replaced with a thermometer and condenser, and 95 g. (0.32 mole) of *cis*-1,2-cyclohexanedimethanol dimethanesulfonate is introduced in one portion (Note 9). The mixture is then stirred at 120° for 18 hours, cooled, and transferred to a 5-l. separatory funnel containing 1500 g. of ice. After 1 l. of hexane is added and the two-phase mixture well shaken, the aqueous phase is reextracted with hexane (500 ml.). The combined organic layers are washed with four 1-l. portions of water, dried over anhydrous magnesium sulfate, and concentrated with a rotary evaporator. The sulfide is collected by bulb-to-bulb distillation at 0.05–0.1 mm. as a colorless liquid (30.8–31.6 g., 68.0–70.5%) (Note 10).

D. *cis*-8-Thiabicyclo[4.3.0]nonane 8,8-dioxide [*benzo*[c]thiophene 2,2-dioxide, *cis*-octahydro-]. A solution of the sulfide (43.0 g., 0.303 mole) in 1 l. of ether is cooled to 0°, stirred magnetically, and treated dropwise with 1.0 l. of 0.65 N ethereal monopero-phthalic acid [*Org. Synth., Coll. Vol. 3, 619 (1955)*]. The mixture is kept overnight at 0°, after which time the precipitated phthalic acid is separated

by filtration and the filtrate is concentrated with a rotary evaporator. Bulb-to-bulb distillation of the residual oil at 0.05–0.1 mm. affords the sulfone as a colorless liquid (48.5–50 g., 92–95%) (Note 11). This product is crystallized from ether-hexane, yielding a colorless solid, m.p. 39–41° (Note 12).

E. *7,9-Dimethyl-cis-8-thiabicyclo[4.3.0]nonane 8,8-dioxide*. A 2-l., one-necked, round-bottomed flask is charged with 800 ml. of anhydrous tetrahydrofuran and 49.0 g. (0.281 mole) of *cis-8-thiabicyclo[4.3.0]nonane 8,8-dioxide*. The solution is blanketed with nitrogen and the flask is fitted with a side-arm adapter having a nitrogen inlet and a rubber septum. The contents are cooled in a 2-propanol–dry ice bath and 225 ml. of 2.5 M *n*-butyllithium in hexane (0.562 mole) is introduced by syringe (Note 13), (Note 14). After 5–10 minutes, 142 g. (1.00 mole) of methyl iodide is added in similar fashion and the cooling bath is removed. Upon warming to room temperature, the reaction mixture is treated slowly with 1 l. of water followed by 1 l. of ether, and the organic layer is separated, washed once with 1 l. of water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The resulting pale-yellow oil (49.5–51 g., 87–89.5%), which consists of a mixture of isomers, is not further purified.

F. *cis-7,8-Dimethylbicyclo[4.2.0]oct-7-ene*. A 1-l., one-necked, round-bottomed flask is charged with 50.5 g. (0.250 mole) of the sulfone from Part E and 200 ml. of dry dioxane (Note 15). The solution is blanketed with nitrogen, and the flask is fitted with a side-arm adapter having a nitrogen inlet and a rubber septum. With ice cooling and magnetic stirring, 150 ml. of 2.5 M *n*-butyllithium in hexane (0.375 mole) is added by syringe (Note 13), (Note 14). The resulting yellow-orange heterogeneous mixture is transferred under nitrogen to a 500-ml., pressure-equalizing dropping funnel and introduced over 25 minutes to a stirred refluxing mixture of lithium aluminum hydride (32.0 g., 0.843 mole) and 2 l. of dry dioxane (Note 16), (Note 17). Upon completion of the addition, the contents are heated at reflux temperature with a mantle for 20 hours, whereupon 100 ml. of saturated aqueous sodium sulfate is added dropwise with cooling (Note 18). The precipitated solids are separated by filtration and washed repeatedly with hexane (Note 19). The combined filtrates are diluted with an additional liter of hexane and washed with four 1-l. portions of water. The organic phase is dried over anhydrous sodium sulfate and carefully concentrated with a rotary evaporator. The residual cyclobutene is purified by distillation, yielding 10.0–12.5 g. (29.5–37%) of colorless oil, b.p. 63–65° (33 mm.) (Note 20), (Note 21).

2. Notes

1. The tetrahydrofuran used in these preparations was distilled from lithium aluminum hydride.
2. A sodium sulfate solution which is not freshly prepared ultimately gives a precipitate of small particle size that is exceedingly difficult and tedious to separate by vacuum filtration.
3. Because the initial reaction is extremely vigorous and exothermic, the first few milliliters must be added very cautiously. In the more advanced stages of this addition the rate of flow may be judiciously increased.
4. Recrystallization of this material from benzene–light petroleum ether gives a pure product, m.p. 42–43°.
5. This reaction is significantly exothermic. Cooling with an acetone–dry ice bath can be employed if desired to expedite the addition of diol. In any event, a temperature in excess of 20° leads to unwanted, rapid hydrolysis and formation of water-soluble by-products.
6. This dimethanesulfonate is reported to have m.p. 75–76°.⁴
7. Sodium sulfide may be conveniently recrystallized from ethanol. Unrecrystallized material may be utilized. However, significantly lower yields will result if the ensuing minor modification is not followed.
8. If unpurified sodium sulfide is employed, a significant quantity of dark insoluble material is seen to adhere to the walls of the flask. Removal of these unwanted contaminants is readily effected by decantation of the hot solution into a second 3-l., three-necked flask before crystallization begins.
9. An exotherm is witnessed and the temperature rises to 70–80°. A color change from yellow to deep purple is also seen; the extent of coloration varies with the purity of the sodium sulfide nonahydrate.
10. The submitters report a yield of 42.0–43.5 g. (93.5–96.8%). The checkers could not reproduce these results in three attempts. This sulfide has also been prepared from the corresponding dibromide.⁶
11. The checkers performed this step on a smaller scale (*ca.* 2/3) and noted (¹H NMR spectrum) occasional contamination (up to 10%) by phthalic anhydride. This impurity causes no subsequent

difficulties. Washing of the crude reaction mixture with cold aqueous sodium hydrogen carbonate resulted in serious product loss because of its appreciable solubility in this medium and, therefore, should be avoided.

12. An earlier report of this sulfone cites a melting point of 39.5–41.0°. ⁶

13. *n*-Butyllithium is available from Ventron Corp.

14. A 50-ml. syringe was employed and a series of transfers was, therefore, necessary.

15. The dioxane was dried before use by distillation from calcium hydride.

16. The apparatus consisted of a 5-l., three-necked, round-bottomed flask equipped with a mechanical stirrer and reflux condenser capped with a nitrogen-inlet tube.

17. The addition rate is such that a gentle reflux is maintained without the need of external heating. Considerable evolution of gas is witnessed.

18. Hydrogen gas is vigorously evolved and the solids ultimately undergo a color change from gray to white.

19. *Caution! Because of the presence of malodorous by-products, it is recommended that the extraction and distillation be conducted in a well-ventilated hood.*

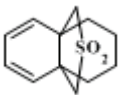
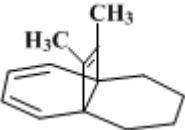
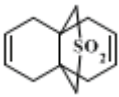
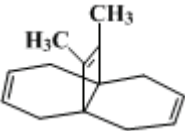
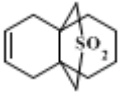
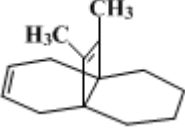
20. The ¹H NMR spectrum (CCl₄) consists of a broad methine signal centered at δ 2.55 and a methyl singlet at δ 1.53 superimposed upon a methylene absorption at δ 1.25–1.85. GC analysis indicated a purity of >98%.

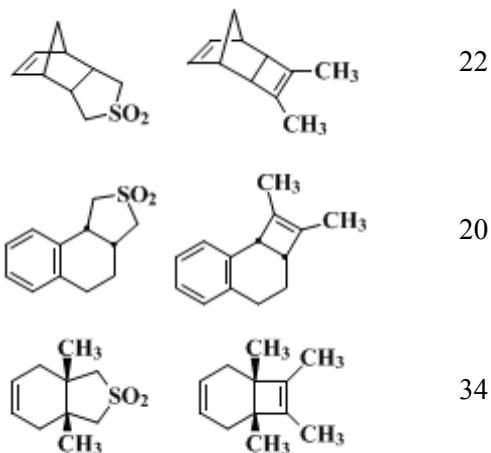
21. The checkers performed this step on one-half scale and obtained comparable results. However, when the product was distilled at higher pressures, b.p. 94–95° (ca. 70 mm.), consistently lower yields were obtained, in the range of 17–18%.

3. Discussion

1-Substituted and 1,2-disubstituted cyclobutenes have previously been prepared by irradiation of 1,3-butadienes capable of photocyclization,^{7,8,9} carbenic decomposition of acylcyclopropane tosylhydrazones,¹⁰ photocycloaddition of α,β -unsaturated ketones to alkynes,¹¹ and reductive ring expansion of cyclopropane 3-carboxylates.¹² However, these and yet other less known methods^{13,14,15,16} lack generality. The present procedure¹⁷ is a versatile scheme which is widely applicable in scope.^{18,19,20} Since a variety of five-membered ring sulfones are readily available from a number of different precursors, the method is fully applicable to a broad spectrum of structural types. Its application to the preparation of mutually stable cyclooctatetraene bond shift isomers is noteworthy.²⁰ The present procedure is illustrative of the general method. Other examples are given in Table I.

TABLE I
REDUCTIVE RING CONTRACTION OF α,α' -
DISUBSTITUTED SULFOLANE ANIONS WITH
LITHIUM ALUMINUM HYDRIDE

Sulfolane	Product	Overall yield, %
		54
		62
		67



Such reductive ring contractions of sulfones are formally similar to two other methods capable of supplanting a sulfur atom by a carbon-carbon double bond: the Ramberg-Bäcklund²¹ and Stevens rearrangements.²² The distinguishing feature of this novel approach to cyclobutenes consists in the resulting higher level of alkyl substitution at the sp²-hybridized centers.

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

Monoperphthalic acid

cis-8-Thiabicyclo[4.3.0]nonane 8,8-dioxide [benzo[c]thiophene 2,2-dioxide, cis-octahydro-]

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium hydrogen carbonate (144-55-8)

sulfone (7446-09-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

phthalic anhydride (85-44-9)

pyridine (110-86-1)

Methyl iodide (74-88-4)

sodium sulfide (1313-82-2)

phthalic acid (88-99-3)

magnesium sulfate (7487-88-9)

dioxane (123-91-1)

butyllithium,
n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

sodium sulfide nonahydrate (1313-84-4)

hexane (110-54-3)

dimethyl sulfoxide (67-68-5)

calcium hydride (7789-78-8)

Methanesulfonyl chloride (124-63-0)

cyclooctatetraene

cis-1,2-cyclohexanedicarboxylic anhydride

Bicyclo[4.2.0]oct-7-ene, 7,8-dimethyl-, cis-,
cis-7,8-Dimethylbicyclo[4.2.0]oct-7-ene (53225-88-0)

cis-1,2-Cyclohexanedimethanol (5059-76-7)

cis-1,2-Cyclohexanedimethanol dimethanesulfonate (66347-68-0)

cis-8-Thiabicyclo[4.3.0]nonane 8,8-dioxide (57479-57-9)

cis-8-Thiabicyclo[4.3.0]nonane (17739-77-4)

7,9-Dimethyl-cis-8-thiabicyclo[4.3.0]nonane 8,8-dioxide (60090-27-9)