



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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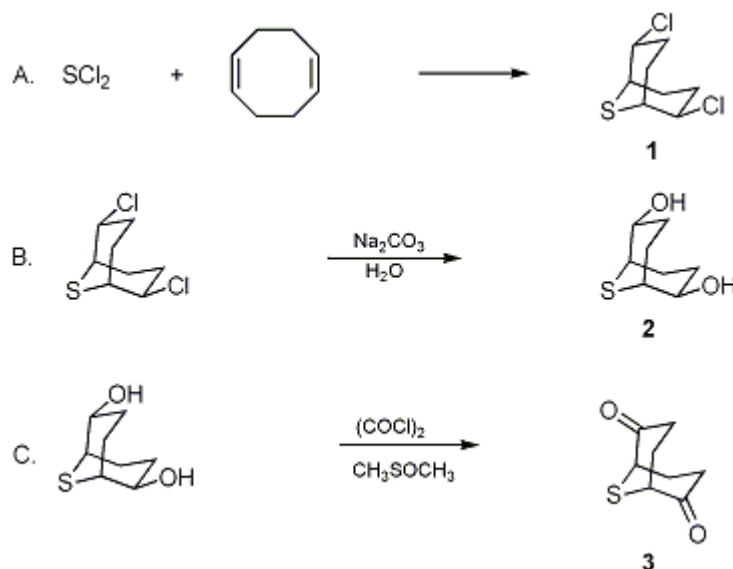
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

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9-THIABICYCLO[3.3.1]NONANE-2,6-DIONE



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1. Procedure

A. *(1 α ,2 α ,5 α ,6 α)-2,6-Dichloro-9-thiabicyclo[3.3.1]nonane (1).* (**CAUTION! Preparation A should be carried out in a well-ventilated hood**). A dry, 2-L, four-necked, round-bottomed flask is equipped with a sealed mechanical stirrer (Note 1), 1-L pressure-equalizing funnel fitted with a drying tube, low temperature thermometer, and a nitrogen inlet. The flask is charged with 125 mL (1.02 mol) of 1,5-cyclooctadiene (Note 2) and 1 L of reagent dichloromethane, cooled to -50 to -60°C using an external acetone-dry ice bath, and the solution placed under a slow stream of dry nitrogen. To the vigorously stirred solution is added slowly over a period of 2 hr a solution of 65 mL (1.02 mol) of freshly purified sulfur dichloride (Note 3) in 500 mL of dichloromethane while maintaining the temperature at, or below, -50°C . The cloudy solution is allowed to warm to room temperature and filtered to remove a small amount of white solid. The filtrate is transferred to a 3-L separatory funnel, washed with brine (3×100 mL), and dried (Na_2SO_4). Solvent is removed from the filtrate under reduced pressure with a rotary evaporator to afford 201.4–210.8 g (94–98%) of *(1 α ,2 α ,5 α ,6 α)-2,6-dichloro-9-thiabicyclo[3.3.1]nonane (1)* as a faintly yellow solid, mp 97.5 – 99°C (Note 4).

B. *(endo,endo)-9-Thiabicyclo[3.3.1]nonane-2,6-diol (2).* To a 1-L, round-bottomed flask, equipped with a magnetic stirring bar, is added 21.12 g (0.10 mol) of the dichloride (1), 100 mL of acetone, and a solution of 34.33 g (0.12 mol) of sodium carbonate decahydrate (Note 5) in 200 mL of water. A condenser is attached to the flask, the contents are stirred gently and then heated to reflux. After 1 hr at reflux (bath temperature ca. 85°C) the clear solution is allowed to cool to room temperature and the stirrer bar is removed (Note 6). Solvent is removed under reduced pressure using a rotary evaporator until the aqueous slurry of white solid is reduced to roughly 25 mL and then the solid is removed by suction filtration at room temperature. The dried, crude diol is heated with 300 mL of methanol and the hot solution filtered directly into a 500-mL, round-bottomed flask, thereby removing small quantities of solid impurity (Note 7). A rotary evaporator is used to concentrate the solution to a volume of ca. 40 mL, and the resulting slurry is filtered to yield 15.2–16.2 g (87–93%) of *(endo,endo)-9-thiabicyclo[3.3.1]nonane-2,6-diol (2)* as a white solid (Note 8), (Note 9).

C. *9-Thiabicyclo[3.3.1]nonane-2,6-dione (3).* (**CAUTION! Oxalyl chloride and dimethyl sulfoxide are reported to react explosively at room temperature. Preparation C should be carried out in a well-**

ventilated hood since a co-product of the reaction is dimethyl sulfide). To a 1-L, three-necked flask equipped with a magnetic stirring bar, low temperature thermometer, dropping funnel protected from moisture by a drying tube, and a second drying tube, is added 13.5 mL (0.16 mol) of oxalyl chloride and 350 mL of dichloromethane. The solution is stirred and cooled to -78°C using an external acetone-dry ice bath. A solution of 22.0 mL (0.31 mol) of dry dimethyl sulfoxide (Note 10) in 75 mL of dichloromethane is added over 10 min ensuring that the reaction temperature does not exceed -60°C . After a further 10 min a solution of 13.07 g (0.08 mol) of (endo,endo)-9-thiabicyclo[3.3.1]nonane-2,6-diol (**2**) in 30 mL of dry dimethyl sulfoxide is added rapidly from the dropping funnel to the stirred solution at -78°C (Note 11). Final traces of the solution are washed into the reaction using a further 10 mL of dry dimethyl sulfoxide. The reaction is stirred for 25 min at -78°C after addition of diol **2** is complete and then 105 mL of redistilled triethylamine is added dropwise. After a further 15 min at -78°C the cooling bath is removed and the reaction is allowed to warm to room temperature whereupon 300 mL of water is added. The material is transferred to a 2-L separatory funnel, the dichloromethane layer is separated, and the aqueous layer is extracted with two 100-mL portions of dichloromethane. The combined dichloromethane extracts are washed successively with 1 L of 1% hydrochloric acid, 300 mL of 5% aqueous sodium carbonate, and two 300-mL portions of water. After the extracts are dried (anhydrous sodium sulfate), the pale yellow filtrate is evaporated to give 11.9–12.4 g of crude 9-thiabicyclo[3.3.1]nonane-2,6-dione (**3**) as a slightly yellow solid. Thin layer chromatography (silica/dichloromethane) indicates the presence of a small quantity of colored polar impurity, which is not easily removed by recrystallization. The crude solid is dissolved in ca. 300 mL of hot 1:1 ethyl ether/benzene containing 0.5 g of activated charcoal, then filtered through a short plug of Celite filter aid. The plug is washed with further hot solvent and the combined filtrates are evaporated to give 11.3–11.7 g (88–92%) of 9-thiabicyclo[3.3.1]nonane-2,6-dione (**3**) as a faintly off-white solid of ca. 99% purity. Analytically pure material is obtained by recrystallization from 2:1 light petroleum/chloroform or from 1:1 light petroleum/dichloromethane. Alternatively, the product is sublimed under reduced pressure (ca. $160^{\circ}\text{C}/30\text{ mm}$) (Note 12).

2. Notes

1. A magnetic stirring bar may be used provided that *vigorous* mixing of the solution is possible.
2. 1,5-Cyclooctadiene purchased from the Aldrich Chemical Company, Inc. was purified by elution of the neat liquid through a short column of activated alumina immediately prior to use.
3. Sulfur dichloride partially decomposes on standing to chlorine and sulfur monochloride and so should always be purified before use. Commercial sulfur dichloride of approximately 80% purity (Aldrich Chemical Company, Inc.) was purified in a hood following the procedure described by Brauer.² Phosphorus trichloride (2 mL) was added to crude sulfur dichloride (200 mL) contained in a flask set up for a standard distillation and protected from the atmosphere by a silica gel drying tube. The fraction boiling between $55\text{--}63^{\circ}\text{C}$ was collected in a receiving flask containing phosphorus trichloride (5 drops). A second distillation using the same technique gave pure sulfur dichloride of bp $59\text{--}60^{\circ}\text{C}/\text{atmospheric pressure}$. Material stabilized with a few drops of phosphorus trichloride may be stored for a few days in a sealed container without significant decomposition.
4. Compound **1** has the following spectral properties. IR (paraffin mull) cm^{-1} : 1245 (m), 1160 (m), 1000 (w), 950 (w), 890 (w), 815 (s), 755 (m), 735 (m); $^1\text{H NMR}$ (CDCl_3) δ : 2.18–2.38 (6 H, m), 2.65–2.70 (2 H, m), 2.85–2.88 (2 H, m), 4.68–4.75 (2 H, m); $^{13}\text{C NMR}$ (CDCl_3) δ : 28.3 (t), 32.6 (t), 37.3 (d), 62.5 (d). The crude product is sufficiently pure for most purposes, but analytically pure material is colorless, lit.³ mp $98.1\text{--}99.6^{\circ}\text{C}$. This may be obtained by trituration of the crude product with a little ethyl ether (which removes a small quantity of yellowish oil) followed by filtration. Alternatively it may be purified by sublimation under reduced pressure ($48^{\circ}\text{C}/0.05\text{ mm}$)³ or recrystallized from benzene.⁴
5. The checkers employed anhydrous sodium carbonate.
6. The checkers filtered the solution at this point to remove small amounts of a brown solid.
7. (endo,endo)-9-Thiabicyclo[3.3.1]nonane-2,6-diol (**2**) is remarkably insoluble in the solvents normally used for extraction of organic materials from aqueous solutions.
8. Compound (**2**) has the following spectral properties. IR (paraffin mull) cm^{-1} : 3300 (s), 1025 (s), 990 (m), 950 (w), 900 (w), 880 (m); $^1\text{H NMR}$ ($\text{d}^6\text{-DMSO}$) δ : 1.55–1.93 (6 H, m), 2.28–2.50 (4 H, m), 3.91 (2 H, m), 4.91 (2 H, d, $J = 6$); $^{13}\text{C NMR}$ ($\text{d}^6\text{-DMSO}$) δ : 26.4 (t), 30.8 (t), 37.0 (d), 70.7 (d).
9. Lautenschlaeger⁵ has reported that diol **2** can be obtained in polymorphic forms with melting points between 188°C and 257°C according to the history of the sample. Determination of the mp is therefore

not necessarily a good indicator of purity in this particular case, and the spectroscopic methods quoted are recommended. Crystals from [methanol](#) had mp 250–253°C (lit.⁴ 249–250.5°C) but these rapidly became opaque and eventually crumbled to a white powder with lower mp. Samples of diol **2** prepared by the method described here melted indistinctly about 220–225°C.

10. [Dimethyl sulfoxide](#) was stirred and heated at ca. 100°C with powdered [calcium hydride](#) for 2 hr, distilled under reduced pressure, and used at once.

11. Care must be taken to ensure that the liquid from the funnel drops directly into the reaction and not onto the walls of the flask where it will solidify.

12. The physical properties of the product are as follows: mp 140–142°C; lit.⁶ 140–142°C. IR (paraffin mull) cm^{-1} : 1690 (s), 1260 (m), 1215 (m), 1125 (m), 1095 (w), 1035 (w), 935 (w); ^1H NMR (CDCl_3) δ : 2.47–2.69 (6 H, m), 2.82–2.89 (2 H, m), 3.37–3.38 (2 H, m); ^{13}C NMR (CDCl_3) δ : 31.1 (t), 36.6 (t), 44.7 (d), 205.2 (s).

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 addition of [sulfur dichloride](#) and [1,5-cyclooctadiene](#) to produce [\(1 \$\alpha\$,2 \$\alpha\$,5 \$\alpha\$,6 \$\alpha\$ \)-2,6-dichloro-9-thiabicyclo\[3.3.1\]nonane \(**1**\)](#) has been described by several workers.^{3,4,5,7} Determination of the stereochemistry of the product has been carried out using ^1H NMR methods,³ and by means of the X-ray crystal structure of the corresponding sulfone derivative.⁸ The procedure described here as step A is that due to Corey and Block.³

Hydrolysis of the dichloride (**1**) to yield [\(endo,endo\)-9-thiabicyclo\[3.3.1\]nonane-2,6-diol \(**2**\)](#) has been carried out using water,⁴ aqueous [sodium hydroxide](#),⁴ aqueous [sodium hydrogen carbonate](#),⁵ and aqueous [sodium carbonate](#).⁵ Step B is an improved version of the latter reaction. The (endo,endo)-stereochemistry was originally inferred from IR evidence,⁴ and subsequently confirmed by NMR work and the crystal structure of the related compound 2,6-dinitrato-9-thiabicyclo[3.3.1]nonane 9,9-dioxide.⁹ Both the high lability of the dichloride (**1**) and the stereochemistry resulting from hydrolysis arise from neighboring group participation of the sulfur atom to form intramolecular sulfonium ion intermediates.^{3,4} These processes have been studied in detail by Vincent and co-workers¹⁰ using ^{13}C NMR spectroscopy.

The [diketone \(**3**\)](#) is a versatile intermediate for the preparation of 9-thiabicyclo[3.3.1]nonane derivatives^{6,11,12,13} and provides a simple synthetic entry to a number of other heterocycles such as the [2-thiaadamantane](#),^{13,14} [thiacyclohexane](#),¹⁵ [thiacycloheptane](#),¹⁵ [2,6-dithiaadamantane](#),¹⁶ and [2-thiabrexane](#)¹⁷ ring systems. Only one previous procedure for its preparation has been published.⁶ This method involves the oxidation of diol (**2**) with [chromium trioxide](#) in [pyridine](#) and [dichloromethane](#) to yield [9-thiabicyclo\[3.3.1\]nonane-2,6-dione \(**3**\)](#) in 65% yield. In practice this reaction is difficult to carry out reproducibly because of precipitation of tarry chromium salts which make adequate stirring and extraction of the product very difficult. Consequently the dione (**3**) is often accompanied by partly oxidized material and/or material where the sulfur atom has been oxidized. The method reported here avoids these technical difficulties and affords a considerably increased yield.

More generally, the procedure described in step C illustrates how the Swern oxidation method^{18,19,20} can be employed for the selective oxidation of an alcohol functionality in the presence of a sulfur moiety. A drawback of the original Swern oxidation is the lack of solubility of some substrates in the [dichloromethane](#) solvent at low temperatures, which results in a serious reduction of yield. In the past this has been avoided by carrying out the oxidation step at -10°C . This once again gave excellent yields, but this procedure required the use of twice the stoichiometric amount of oxidant.¹⁹ The method described here as step C demonstrates that this is not necessary, and that the oxidation of insoluble materials can be carried out following the routine procedure provided that the substrate is added as a solution in dry [dimethyl sulfoxide](#).

Step C has been carried out on three times the described scale without any deleterious effects being

noted.

References and Notes

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Appendix

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

silica

brine

2,6-dinitrato-9-thiabicyclo[3.3.1]nonane 9,9-dioxide

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ethyl ether (60-29-7)

diketone (107-22-2)

sodium hydroxide (1310-73-2)

sodium hydrogen carbonate (144-55-8)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

acetone (67-64-1)

pyridine (110-86-1)

chlorine (7782-50-5)

phosphorus trichloride (7719-12-2)

sodium carbonate decahydrate (6132-02-1)

sulfur monochloride

dichloromethane (75-09-2)

chromium trioxide (1333-82-0)

sulfur dichloride (10545-99-0)

dimethyl sulfide (75-18-3)

oxalyl chloride (79-37-8)

dimethyl sulfoxide (67-68-5)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

1,5-cyclooctadiene

9-Thiabicyclo[3.3.1]nonane-2,6-dione (37918-35-7)

(endo,endo)-9-Thiabicyclo[3.3.1]nonane-2,6-diol (22333-35-3)

2-thiaadamantane (281-25-4)

thiacyclohexane (1613-51-0)

thiacycloheptane (4753-80-4)

2,6-dithiaadamantane

(1 α ,2 α ,5 α ,6 α)-2,6-Dichloro-9-thiabicyclo[3.3.1]nonane (10502-30-4)

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