Organic Syntheses

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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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.

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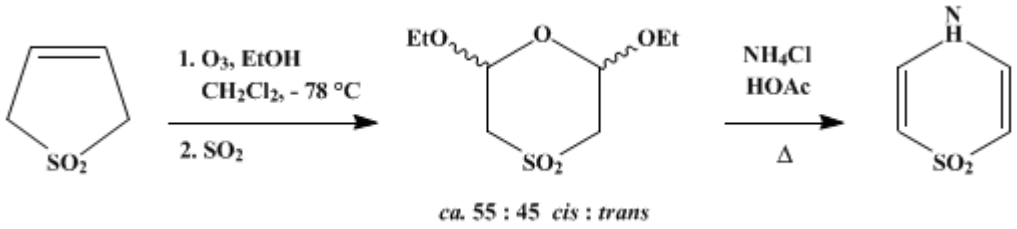
4*H*-1,4-THIAZINE 1,1-DIOXIDE



ca. 55 : 45 *cis* : *trans*

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1. Procedure

Caution! Ozone is extremely toxic and can react explosively with certain oxidizable substances. Ozone also reacts with some compounds to form explosive and shock-sensitive products. Ozone should only be handled by individuals trained in its proper and safe use and all operations should be carried out in a well-ventilated fume hood behind a protective safety shield. [Note added September 2009].

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. cis *and* trans-2,6-*Diethoxy*-1,4-*oxathiane* 4,4-*dioxide*. Ozone (Note 1) is passed into a solution of 2,5-dihydrothiophene 1,1-dioxide (30.0 g., 0.254 mole) (Note 2) in 50 ml. of absolute ethanol (Note 3) and 250 ml. of dichloromethane contained in a 1-l., three-necked, round-bottomed flask fitted with a straight glass-inlet tube, a calcium chloride drying tube, and a glass stopper. The solution is cooled in a methanol–dry ice bath and magnetically stirred while the ozone is added. When the solution becomes blue (Note 4), the addition of ozone is stopped and liquid sulfur dioxide (35 ml., 0.78 mole) (Note 5) is added in portions over a period of 10–15 seconds. After 2 minutes, the cold bath is removed and the reaction solution is allowed to warm to room temperature over a period of 8–16 hours. The resulting dark-brown solution is poured into a 4-l. beaker containing a rapidly stirred mixture of aqueous sodium carbonate (120 g. in 1 l. of cold water) and 200 g. of ice. The reaction flask is rinsed with 50 ml. of water, which is added to the basic mixture. After being stirred for 5 minutes, the basic mixture is poured into a 2-l. separatory funnel and the lower dichloromethane layer is separated and saved. The beaker is rinsed with 200 ml. of dichloromethane and 100 ml. of water, which are then added to the separatory funnel. The contents of the separatory funnel are shaken, and the lower, dichloromethane layer is separated and saved. The aqueous layer is extracted with two more 150-ml. portions of dichloromethane. All of the dichloromethane layers and extracts are combined, and washed with 300 ml. of water and 300 ml. of saturated aqueous sodium chloride. The solution is dried over 3–6 g. of anhydrous magnesium sulfate, filtered, and evaporated with a rotary evaporator at 50–60° in a water bath under aspirator pressure. The residual, cream-colored solid (50–52 g., 88–91%), m.p. 76–118°, is dissolved with magnetic stirring in 850–950 ml. of boiling heptane (Note 6) containing 1–2 g. of activated carbon and filtered hot.

The filtrate is cooled to 0° in a refrigerator overnight. The resulting precipitate is filtered, giving *cis*- and *trans*-2,6-diethoxy-1,4-oxathiane 4,4-dioxide as a white solid (42–46 g., 74–81%), m.p. 83–117° (Note 7).

B. 4*H*-1,4-*Thiazine* 1,1-*dioxide*. *Caution! This step should be carried out in a hood to avoid exposure to hydrogen chloride gas.* A mixture of *cis*- and *trans*-2,6-diethoxy-1,4-oxathiane 4,4-dioxide (15.0 g., 0.0669 mole), 3.8 g. (0.071 mole) of ammonium chloride (Note 8), and 300 ml. of glacial acetic acid is placed in a 500-ml., one-necked, round-bottomed flask fitted with a reflux condenser and a magnetic stirring bar. The mixture is placed in an oil bath preheated to 125–130° and refluxed, with magnetic stirring, for 25–35 minutes, during which the ammonium chloride dissolves, hydrogen chloride is evolved, and the solution becomes brownish yellow in color (Note 9). The acetic acid is evaporated with a rotary evaporator at 70–80° in a water bath under aspirator pressure. The residual yellow solid is magnetically stirred with a solution of 75 ml. of diethyl ether containing 10 ml. of 2-propanol for 10 minutes (Note 10). The resulting suspension is filtered, then sucked dry on a Büchner funnel. The yellow solid (8.7–9.2 g.), m.p. 208–212°, is boiled with 225–250 ml. of 2-propanol and filtered hot, removing the residual, greenish-black, insoluble material (0.5–1 g.). The filtrate is cooled to −10° to −5° in a freezer overnight, causing separation of 4.6–5.3 g. (52–60%) of 4*H*-1,4-thiazine

1,1-dioxide as small yellow needles, m.p. 237–240° (Note 11), which are filtered. Concentration of the filtrate to 50 ml., followed by filtration and cooling, causes separation of an additional 1.5–2.0 g. (17–23%) of crude yellow solid, m.p. 234–240°.

2. Notes

1. A Welsbach Corporation Ozonator, style T-23, was used, with the voltage set at 120 volts and the oxygen pressure at 8 p.s.i. to give a 4–5% ozone concentration. The checkers used a Welsbach Corporation Ozonator, style T-408, to give a 1–2% ozone concentration. The input oxygen was dried by being passed through a tower of color-indicating Hammond Drierite.

2. 2,5-Dihydrothiophene 1,1-dioxide (butadiene sulfone, or 3-sulfolene) was purchased from the Aldrich Chemical Company, Inc.

3. Use of larger amounts of absolute ethanol causes formation of more of the acyclic 3-thiapentane-1,5-dial bis(diethyl acetal) 3,3-dioxide, with a corresponding reduction in yield of the cyclic product.

4. Appearance of the blue color of ozone signals complete cleavage of the double bond. Further addition of ozone could cause undesirable oxidation.

5. Sulfur dioxide was purchased in lecture-size bottles from the City Chemical Corporation. The gas was condensed into a precalibrated, 50-ml. Erlenmeyer flask cooled in the methanol–dry ice bath used for cooling the ozonolysis reaction.

6. Eastman Organic Chemicals Technical Grade "Heptanes," b.p. 96–100°, containing 70% heptanes and the rest octanes, was used.

7. In one instance the submitters obtained an 85% yield when the reaction mixture was stirred with sulfur dioxide for 18 hours, followed by crystallization of the resulting crude material (32 g. per l.) without the use of charcoal.

The product is obtained as an approximately 55:45 mixture of *cis*- and *trans*-isomers, as indicated by ^{1}H NMR absorption ($CDCl_3$) at δ 1.27 (t, J = 7 Hz., 5.9H, 2 OCH_2CH_3), 2.77–3.47 (m, 4.0H, $CH_2SO_2CH_2$), 3.47–4.27 (m, 4.1H, 2 OCH_2CH_3), 4.95 (d of d, $J_{a,a}$ = 8 Hz., $J_{a,e}$ = 2 Hz., 1.1H, C*H* proton of the *cis*-isomer), and 5.33 (t, J = 4 Hz., 0.9H, C*H* proton of the *trans*-isomer). The IR spectrum (Nujol) has strong bands at 1312, 1118, 1029, and 972 cm.$^{-1}$, which are attributed to the SO_2 and CO groups. The *cis*-isomer, m.p. 103–105°, can be separated from the mixture by three or four fractional crystallizations from methanol, while the *trans*-isomer, m.p. 136–137°, can be separated from the mixture (or from the residue obtained by evaporation of the methanol mother liquors from which the *cis*-isomer was crystallized) by two or three fractional crystallizations from benzene-petroleum ether (b.p. 60–68°).

8. "Baker Analyzed" Reagent Grade ammonium chloride was purchased from the J. T. Baker Chemical Company.

9. Refluxing for longer times causes formation of increased amounts of a dark, greenish-brown by-product, which complicates purification by crystallization. If the acetic acid becomes black-brown, the residue (which is sometimes tarry) obtained on evaporation can be purified by rapid chromatography through a 3.8-cm.-deep column of activated alumina, using acetone as a transfer agent and eluent.

10. The purpose of the wash with ether and 2-propanol is to remove the remaining acetic acid and any residual hydrogen chloride, which may cause decomposition during the subsequent crystallization.

11. The analytical sample melted at 240–241.5°. The IR spectrum (Nujol) has a strong NH band at 3360, a strong band in the double bond region at 1645 and another at 1511, and a group of bands at 1265 and 1255 (medium strong) and 1238, 1226, 1102, and 1093 (all strong), some of which are attributable to the sulfonyl group, and a strong band at 692 cm.$^{-1}$. The ^{1}H NMR spectrum (dimethyl sulfoxide-d_6) has an AA'BB' pattern with major peaks at δ 7.12 and 6.99 (2.0H) and 6.02 and 5.88 (2.0H), attributed to the 4 C*H* protons. The UV spectrum has maxima (95% C_2H_5OH) nm at (log ε) 226 (3.75), 230, inflection (3.72), 237, inflection (3.47), 277 (3.52), and 287 (3.55).

3. Discussion

This procedure represents the first reported synthesis of *cis*- and *trans*-2,6-diethoxy-1,4-oxathiane 4,4-dioxide[3] and of its further reaction product, 4*H*-1,4-thiazine 1,1-dioxide.[3] A derivative of the latter, 3,5-diphenyl-4*H*-1,4-thiazine 1,1-dioxide, has been prepared previously by reaction of phenacyl sulfone with ammonia.[4,5] Primary amines, in addition to ammonia, can be converted to the corresponding 4-substituted 4*H*-1,4-thiazine 1,1-dioxides by condensation with 2,6-diethoxy-1,4-oxathiane 4,4-dioxide, using the procedure described above. For example, 4-aminobenzoic acid hydrochloride gave 4-(4-carboxyphenyl)-4*H*-1,4-thiazine 1,1-dioxide in 83% yield.[3] The submitters have also observed,[3] as have others,[4] that the 4*H*-1,4-thiazine 1,1-dioxide system may be *N*-alkylated with an alkyl halide using potassium carbonate in anhydrous acetone.

The ozonolysis reaction, followed by reductive workup with sulfur dioxide, as described in Part A of the present

procedure, illustrates a general method which has been developed for the preparation of acetals.[3] Application of the procedure is illustrated by conversion of the following olefins in alcoholic solution to the corresponding acetals:[3] (1) 1-chloro-4-(2-nitrophenyl)-2-butene to 2-nitrophenylacetaldehyde dimethyl acetal in 84% yield; (2) 1,4-dibromo-2-butene to bromoacetaldehyde dimethyl acetal in 67% yield; (3) 3-butenoic acid to malonaldehydic acid diethyl acetal ethyl ester in 61% yield; (4) cyclopentadiene to malonaldehyde bis(diethyl acetal) in 48% yield; and (5) 1,4-dinitro-2-butene (produced *in situ* from 1,3-butadiene and dinitrogen tetroxide) to nitroacetaldehyde diethyl acetal in 21% yield.

References and Notes

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2. Safety and Security Systems Laboratory, 3M Company, St. Paul, Minnesota 55101.
3. Robert D. DeMaster, Ph.D. Dissertation, University of Minnesota, Minneapolis, Minnesota, June 1970 [*Diss. Abstr. Int. B*, **31**, 5871 (1971)].
4. C. R. Johnson and I. Sataty, *J. Med. Chem.*, **10**, 501 (1967).
5. I. Sataty, *J. Org. Chem.*, **34**, 250 (1969).

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

benzene-petroleum ether

dinitrogen tetroxide

butadiene sulfone

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrogen chloride (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

Benzene (71-43-2)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sulfur dioxide (7446-09-5)

oxygen (7782-44-7)

acetone (67-64-1)

carbon (7782-42-5)

2-propanol (67-63-0)

dichloromethane (75-09-2)

ozone (10028-15-6)

magnesium sulfate (7487-88-9)

1,3-Butadiene (106-99-0)

heptane (142-82-5)

3-Butenoic acid (625-38-7)

CYCLOPENTADIENE (542-92-7)

malonaldehyde bis(diethyl acetal) (122-31-6)

3-thiapentane-1,5-dial bis(diethyl acetal) 3,3-dioxide

phenacyl sulfone

2,6-diethoxy-1,4-oxathiane 4,4-dioxide,
cis and trans-2,6-Diethoxy-1,4-oxathiane 4,4-dioxide,
cis- and trans-2,6-diethoxy-1,4-oxathiane 4,4-dioxide (40263-59-0)

4-aminobenzoic acid hydrochloride

1-chloro-4-(2-nitrophenyl)-2-butene

2-nitrophenylacetaldehyde dimethyl acetal

1,4-dibromo-2-butene

bromoacetaldehyde dimethyl acetal (7252-83-7)

malonaldehydic acid diethyl acetal ethyl ester

Nitroacetaldehyde diethyl acetal (34560-16-2)

3-sulfolene,
2,5-dihydrothiophene 1,1-dioxide

4H-1,4-Thiazine 1,1-dioxide (40263-61-4)

3,5-diphenyl-4H-1,4-thiazine 1,1-dioxide

4H-1,4-thiazine

4-(4-carboxyphenyl)-4H-1,4-thiazine 1,1-dioxide

1,4-dinitro-2-butene