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Working with Hazardous Chemicals

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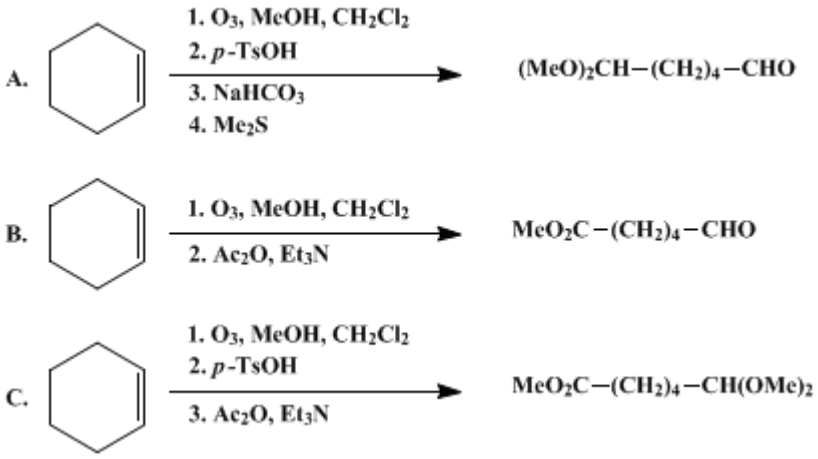
DOI:10.15227/orgsyn.064.0150

Organic Syntheses, Coll. Vol. 7, p.168 (1990); Vol. 64, p.150 (1986).

OZONOLYTIC CLEAVAGE OF CYCLOHEXENE TO TERMINALLY DIFFERENTIATED PRODUCTS: METHYL 6-OXOHEXANOATE, 6,6-DIMETHOXYHEXANAL, METHYL 6,6-DIMETHOXYHEXANOATE

[Hexanoic acid, 6-oxo-, methyl ester; hexanal, 6,6-dimethoxy-; hexanoic acid, 6,6-dimethoxy-, methyl ester]



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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.

A. A 500 mL, three-necked, round-bottomed flask is fitted with a glass tube to admit ozone, a calcium chloride drying tube, a glass stopper, and a magnetic stirring bar and is charged with 6.161 g of cyclohexene (0.075 mol), 250 mL of dichloromethane, and 50 mL of methanol (Note 1). The flask is cooled to ca. −78°C (2-propanol–dry ice), and ozone (Note 2) is bubbled through the solution with stirring. When the solution turns blue, ozone addition is stopped. Nitrogen is passed through the solution until the blue color is discharged (Note 3) and then the cold bath is removed. The drying tube and ozone inlet are replaced with a stopper and rubber septum, and 1.215 g of *p*-toluenesulfonic acid (TsOH) (10% w/w) (Note 4) is added. The solution is allowed to warm to room temperature as it stirs under an atmosphere of nitrogen for 90 min. Anhydrous sodium bicarbonate (2.147 g, 4 mol-equiv) is added to the flask and the mixture is stirred for 15 min, and then 12 mL of dimethyl sulfide (0.150 mol) (Note 5) is added. After being stirred for 12 hr, the heterogeneous mixture is concentrated to approximately 50 mL by rotary evaporation. Dichloromethane (100 mL) is added and the mixture is washed with 75 mL of water (Note 6). The aqueous layer is extracted with two more 100-mL portions of dichloromethane, and the combined organic layers are washed with 100 mL of water. After extracting the aqueous layer with 100 mL of dichloromethane, the organic layers are dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation. Short-path distillation of the crude product (Note 7) gives 8.2–8.4 g of 6,6-dimethoxyhexanal, 68–70%, bp 80–82°C/1.75 mm (Note 8) and (Note 9).

B. A round-bottomed flask equipped as in Step A is charged with 6.161 g of cyclohexene (0.075 mol), 250 mL of dichloromethane, 50 mL of methanol, and 2.0 g of anhydrous sodium bicarbonate (Note 1) and (Note 10). After the apparatus is cooled to ca. −78°C. ozone (Note 2) is bubbled through the solution as it is stirred. Ozone addition is stopped when the solution turns blue. Nitrogen is passed through the solution until the blue color is discharged (Note 3) and then the cold bath is removed. The solution is filtered into a l-L, round-bottomed flask and 80 mL of benzene is added. The volume is reduced to approximately 50 mL by rotary evaporation (Note 11). After dilution with 225 mL of dichloromethane the flask is cooled to 0°C and 16 mL of triethylamine (0.113 mol) and 21.24 mL of acetic anhydride (0.225 mol) are added via syringe (Note 12), and the solution is stirred under a nitrogen atmosphere for 15 min. The ice bath is removed and stirring

is continued for 4 hr. The solution is washed with 150-mL portions of aqueous 0.1 *N* hydrochloric acid, aqueous 10% sodium hydroxide, and water. The organic layer is dried over anhydrous magnesium sulfate and filtered, and the solvent is removed by rotary evaporation. Short-path distillation of the crude product yields methyl 6-oxohexanoate, (7.0–7.8 g, 65–72%), bp 83–86°C/1.5 mm (Note 13).

C. Cyclohexene, 6.161 g (0.075 mol), is stirred with ozone in dichloromethane and methanol, as above. The resulting solution is treated with *p*-toluenesulfonic acid and subsequently neutralized with sodium bicarbonate, as described in Procedure A. The solution is filtered into a 1-L, round-bottomed flask, 80 mL of benzene is added, and the volume is reduced to approximately 50 mL by rotary evaporation (Note 11). Dilution with dichloromethane, treatment with triethylamine and acetic anhydride, and workup as described in Procedure B followed by short-path distillation provides methyl (6,6-dimethoxy)hexanoate, (11.2–11.8 g, 78–83%), bp 87–91°C/1.5 mm (Note 14).

2. Notes

1. Cyclohexene was purchased from Aldrich Chemical Company, Inc. and used without purification. Dichloromethane was distilled from calcium hydride. Methanol was distilled from magnesium. The methanol–dichloromethane solvent combination may be replaced with 100% methanol (250 mL) with comparable results.

2. Ozone was produced by a Welsbach Corporation Ozonator, style T-709, with the voltages set at 100 V and oxygen pressure at 7 psi to give approximately 2% ozone concentration. The input oxygen was passed through a column of Hammond Drierite to ensure dryness.

3. The blue color indicates that cleavage of the olefin is complete. Excess ozone is removed to prevent overoxidation

4. Although the ozonolysis product exists in oligomeric form, the amount of acid used was calculated by assuming a theoretical yield of the corresponding monomeric aldehyde–methoxy hydroperoxide. *p*-Toluenesulfonic acid monohydrate, purchased from Aldrich Chemical Company, Inc., was not purified further.

5. The solution is neutralized to prevent bisacetal formation on subsequent reduction. Dimethyl sulfide was purchased from Aldrich Chemical Company, Inc. and used without purification.

6. An aqueous workup facilitates the removal of dimethyl sulfoxide produced by the reduction of the peroxide.

7. Typically 12.4–13.0 g of crude product is obtained after solvent removal. Material of this quality is satisfactory for most subsequent reactions.

8. The distilled product is similar in purity to the crude material. A small amount of dimethyl sulfoxide and minor impurities remain. Purification of the crude product by flash chromatography (1:1 ether:hexanes) affords 6,6-dimethoxyhexanal that is pure by ^{1}H and ^{13}C NMR in 90–95% yield.

9. The following spectral properties of the product were observed: ^{1}H NMR ($CDCl_3$), δ: 1.4–1.7 (m, 6 H), 2.4 (t, 2 H, $J = 7$), 3.3 (s, 6 H), 4.3 (t, 1 H, $J = 5.3$), 9.7 (t, 1 H, $J = 2.5$). ^{13}C NMR ($CDCl_3$), δ: 21.4, 23.7, 31.8, 43.2, 52.1, 103.9, 201.6. IR (film), cm^{-1}: 2700, 1720, 1100. MS, *m/e* (rel. %): 113(95), 57(100).

10. Sodium bicarbonate serves to buffer the solution and prevent acetal formation.

11. Benzene is added to facilitate the removal of methanol. Although an aqueous wash will remove the methanol, azeotropic removal with benzene is simpler and provides a slightly higher yield.

12. Triethylamine purchased from Aldrich Chemical Company, Inc., was distilled from calcium hydride. Acetic anhydride as supplied by Mallinckrodt, Inc. was distilled from phosphorus pentoxide.

13. The following spectral properties were observed: ^{1}H NMR ($CDCl_3$), δ: 1.5–1.7 (m, 4 H), 2.2–2.4 (m, 4 H), 3.6 (s, 3 H), 9.7 (t, 1 H, $J = 2.5$). ^{13}C NMR ($CDCl_3$), δ: 21.1, 24.0, 33.2, 42.9, 51.0, 173.1, 201.4. IR (film), cm^{-1}: 2700, 1720, 1150. MS: *m/e* (rel. %): 159(1), 29(3), 75(100).

14. The following spectral properties were observed: ^{1}H NMR ($CDCl_3$), δ: 1.0–1.6 (m, 6 H), 2.15 (t, 2 H, $J = 8$), 3.2 (s, 6 H), 3.6 (s, 3 H), 4.25 (t, 1 H, $J = 5.5$). ^{13}C NMR ($CDCl_3$), δ: 23.7, 24.3, 31.8, 33.4, 50.7, 52.0, 103.9, 173.1. IR (film), cm^{-1}: 1735, 1050, MS: *m/e* (rel. %): 159(10), 127(30), 75(100).

3. Discussion

This procedure illustrates a recently published method for the ozonolytic cleavage of cycloalkenes to terminally differentiated products.[2] Other examples of the unsymmetrical cleavage of olefins have been reported.[3] In addition, the title compounds have been prepared by other routes. Methyl 6-oxohexanoate has been synthesized from the acid chloride of the half-ester of adipic acid.[5] It has also been prepared from ε-caprolactone by methanolysis followed by oxidation.[5] Lead tetraacetate treatment of 2-hydroxycyclohexanone in methanol and subsequent acidification produces methyl 6,6-dimethoxyhexanoate.[6] A three-step route from cyclohexanone enol acetate (ozonolysis in methanol and reaction with

dimethyl sulfide, then with trimethyl orthoformate) has been reported.[4] 6,6-Dimethoxyhexanal has been made by a multistep route.[7].

The present method utilizes commercially available cycloalkenes and proceeds under mild conditions to provide synthetically useful products. The method was shown to be general in the series of cycloalkenes investigated. Yields range from moderate (cyclopentene) to excellent (higher homologues).

The ozonolytic cleavage of cycloalkenes in the presence of methanol produces a chain with an aldehyde and a methoxy hydroperoxide group at the termini.[8] The unsymmetrical ozonolysis product is manipulated in several ways. Dehydration of the methoxy hydroperoxide group affords an ester (Step B). Alternatively, the aldehyde moiety is protected as an acetal. Under these conditions, the methoxy hydroperoxide is reduced[9] (Procedure A) or dehydrated (Step C).

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 18

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

p-toluenesulfonic acid (TsOH)

ACETAL (105-57-7)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

magnesium (7439-95-4)

Adipic acid (124-04-9)

Cyclohexene (110-83-8)

oxygen (7782-44-7)

nitrogen (7727-37-9)

dichloromethane (75-09-2)

ozone (10028-15-6)

magnesium sulfate (7487-88-9)

Cyclopentene (142-29-0)

dimethyl sulfide (75-18-3)

dimethyl sulfoxide (67-68-5)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

2-hydroxycyclohexanone

p-toluenesulfonic acid (104-15-4)

trimethyl orthoformate (149-73-5)

Methyl 6-oxohexanoate,
Hexanoic acid, 6-oxo-, methyl ester (6654-36-0)

6,6-Dimethoxyhexanal,
hexanal, 6,6-dimethoxy- (55489-11-7)

hexanoic acid, 6,6-dimethoxy-, methyl ester,
methyl (6,6-dimethoxy)hexanoate,
Methyl 6,6-dimethoxyhexanoate (25176-55-0)

ε-caprolactone (502-44-3)

cyclohexanone enol acetate

phosphorus pentoxide (1314-56-3)

p-toluenesulfonic acid monohydrate (6192-52-5)

lead tetraacetate (546-67-8)