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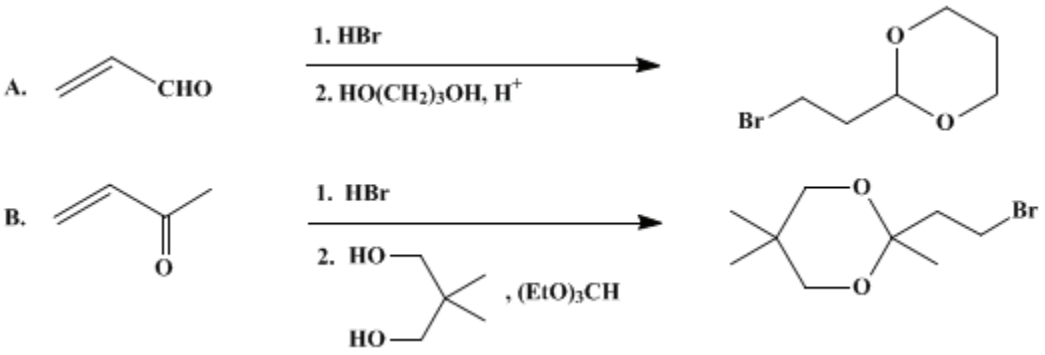
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.062.0140

Organic Syntheses, Coll. Vol. 7, p.59 (1990); Vol. 62, p.140 (1984).

β-HALOACETALS AND KETALS: 2-(2-BROMOETHYL)-1,3-DIOXANE AND 2,5,5-TRIMETHYL-2-(2-BROMOETHYL)-1,3-DIOXANE



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Checked by Yumi Nakagawa and Robert V. Stevens.

1. Procedure

A. *2-(2-Bromoethyl)-1,3-dioxane* (**1**). A 2-L, three-necked flask is equipped with a mechanical stirrer, thermometer, and gas inlet tube. In the flask are placed 750 mL of dichloromethane, 112 g (2.00 mol) of acrolein (Note 1), and 0.10 g of dicinnamalacetone indicator (Note 2) under nitrogen. The yellow solution is cooled to 0–5°C with an ice bath. Gaseous hydrogen bromide (Note 3) is bubbled into the solution with stirring until the indicator becomes deep red (Note 4). The ice bath is removed and 1.0 g of *p*-toluenesulfonic acid monohydrate and 152.2 g (2.00 mol, 144 mL) of 1,3-propanediol (Note 1) are added. The yellow solution is stirred at room temperature for 8 hr and then concentrated with a rotary evaporator. The residual oil is washed with two 250-mL portions of saturated aqueous sodium bicarbonate and dried over anhydrous potassium carbonate. Vacuum distillation through a 30-cm Vigreux column yields 252 g (65%) of **1** as a colorless liquid, bp 72–75°C (2.0 mm), n_D^2 1.4809 (Note 5).

B. *2,5,5-Trimethyl-2-(2-bromoethyl)-1,3-dioxane* (**2**). A 1-L, three-necked flask is equipped with a magnetic stirrer and a gas inlet tube. In the flask are placed 700 mL of dichloromethane, 140 g (2.00 mol) of methyl vinyl ketone (Note 6), and 0.010 g of dicinnamalacetone indicator (Note 2). Anhydrous hydrogen bromide (Note 3) is bubbled into the solution with stirring until the indicator changes to deep red (Note 7). The gas inlet tube is removed and 208 g (2.00 mol) of neopentanediol, 296 g (2.00 mol) of triethyl orthoformate, and 0.67 g of *p*-toluenesulfonic acid monohydrate are added to the solution. The flask is stoppered and stirred at room temperature for 1–2 hr and then concentrated by rotary evaporation (Note 8). The concentrated solution is washed twice with saturated sodium bicarbonate solution. *(Caution! There is some foaming.)* The bicarbonate washes are extracted three times with dichloromethane and the combined organic portions dried over anhydrous K_2CO_3. Rotary evaporation followed by vacuum distillation of the residue through a 30-cm Vigreux column yields 256 g (54%) of **2** as a clear, colorless oil, bp 65°C (0.3 mm), n_D^3 1.4687 (Note 9).

2. Notes

1. The acrolein, 1,3-propanediol, and cinnamaldehyde were purchased from Aldrich Chemical Company, Inc.
2. The indicator was prepared by the method of Diehl and Einhorn.[4] A solution of 5 g of sodium hydroxide in 50 mL of water and 40 mL of ethanol is prepared in a 250-mL Erlenmeyer flask. To this is added a solution of 1.84 mL (0.025 mol, 1.45 g) of acetone in 6.3 mL (0.050 mol, 6.6 g) of freshly distilled cinnamaldehyde (Note 1). This mixture is stirred thoroughly at room temperature for 30 min.

The resulting voluminous yellow precipitate is filtered with suction, washed with 100 mL of water, and dried, affording 6.5 g of 1,9-diphenylnona-1,3,6,8-tetraen-5-one. Recrystallization from 200 mL of hot 95% ethanol gives 3.5 g of yellow crystals, mp 142–143°C (lit.[4] mp 142°C). This indicator is also available from Aldrich Chemical Co.

3. The anhydrous hydrogen bromide was purchased in a lecture bottle from Matheson. A trap is used between the lecture bottle and the gas inlet tube.

4. When the red color persists 5 min after the hydrogen bromide has been turned off, the addition is finished. At this point the proton magnetic resonance spectrum shows only dichloromethane and 3-bromopropanal (60 MHz, CH_2Cl_2) δ: 3.04 (t, 2 H), 3.59 (t, 2 H), 10.67 (s, 1 H).

5. Product **1** has the following spectral characteristics: IR (neat) cm $^{-1}$: 2980, 2870, 1250, 1150, 1140, 1015; ^{1}H NMR (90 MHz, $CDCl_3$) δ: 1.38 (d of m, 1 H, one 5-position on dioxane ring), 1.8–2.4 (m, the other 5-position on the dioxane ring), 2.14 (d of t, 2 H, CH_2-C-Br), 3.45 (t, 2 H, CH_2Br), 3.80 (d of t, 2 H, 4, and 6-positions on ring), 4.15 (d of double d, 2 H, 4, and 6-positions on ring), 4.71 (t, 1 H, 2-position on ring; ^{13}C magnetic resonance (22.5 MHz, $CDCl_3$) δ: 100.06, 66.86, 38.08, 27.79, 25.79.

6. The neopentanediol and triethyl orthoformate were purchased from Aldrich Chemical Co., Inc. and used as received. Failure to distill the methyl vinyl ketone, also obtained from Aldrich Chemical Co. Inc., to a clear, colorless liquid before use resulted in difficulty in determining the endpoint of the reaction with HBr. Therefore, the methyl vinyl ketone was distilled prior to use at reduced pressure.

7. When the red color persists 5 min after the hydrogen bromide has been turned off, the addition is finished. At this point the proton magnetic resonance spectrum shows only dichloromethane and 4-bromo-2-butanone (60 MHz, CH_2Cl_2) δ: 2.15 (s, 3 H, CH_3CO), 3.02 (t, 2 H, CH_2CO), 3.52 (t, 2 H, CH_2Br); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ: 25.75, 30.11, 45.91, 205.12. Little or no exotherm is noticed during the hydrogen bromide addition.

8. The reaction can be conveniently monitored by TLC using silica plates and eluting with 1 : 4 ethyl acetate–heptane.

9. Product 2 has the following characteristics: IR (neat liquid) cm^{-1}: 2970, 2880, 1260, 1220, 1125, 1085; ^{1}H NMR (60 MHz, $CDCl_3$) δ: 0.81 (s, 3 H, 5-methyl), 1.01 (s, 3 H, 5-methyl), 1.34 (s, 3 H, 2-methyl), 2.05–2.45 (m, 2 H, CH_2-C-Br), 3.2–3.8 (m, 6 H, CH_2O and CH_2Br); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ: 19.64, 22.24, 22.76, 26.99, 29.72, 43.25, 70.23, 98.26.

3. Discussion

Cyclic β-haloacetals and ketals have been prepared by variations of two basic methods. The most frequently used method involves the combination of an α,β-unsaturated carbonyl compound (acrolein, methyl vinyl ketone, crotonaldehyde, etc.) a diol, and the anhydrous hydrogen halide. All possible sequences of combining these three have been used. In most cases the anhydrous acid was dissolved in the diol and then the carbonyl compound was added slowly.[5,6] Alternatively, the acetals of the α,β-unsaturated carbonyl compounds were prepared and isolated and then the hydrogen halide was added.[7] Finally the hydrogen halide may be added to the α,β-unsaturation followed by acetal formation,[8] and this is the basis of the present procedures.

The second general method is the aluminum halide-catalyzed reaction of acid halides with ethylene to give β-halo ketones, which are subsequently converted to ketals.[9,10]

The preparations are much simplified if a stoichiometric amount of hydrogen halide is added using an indicator to determine the endpoint. We have found that 1,9-diphenylnona-1,3,6,8-tetraen-5-one (dicinnamalacetone)[11] is of appropriate basicity to detect excess anhydrous hydrogen halides in organic solvents including chloroform, dichloromethane, benzene, toluene, acetic acid, and acetone (but not in alcohols). The reaction between the hydrogen halide and the α,β-unsaturated carbonyl compound is fast enough at 0–25°C that the endpoint is readily detected, and the yield-lowering use of excess hydrogen halide or long contact times[12] are avoidable. The intermediate β-halo aldehydes are unstable toward trimerization[13] if they are not diluted by a solvent and therefore should not be isolated but used directly in the next step. β-Bromo ketones darken on isolation and brief storage, so they, too, should be protected directly.

The conversion of the intermediate bromo aldehyde to the dioxane proceeds readily because of a favorable equilibrium position. However, the equilibrium for the reaction of the bromo ketone with the

diol is unfavorable and requires removal of the by-product, water. This is done under mild conditions using ethyl orthoformate.[14]

We have chosen to use 1,3-diols because the Grignard reagents derived from the 1,3-dioxanes are thermally stable.[15] This contrasts with the use of ethylene glycol where the resulting β-haloalkyl dioxolanes give Grignard reagents that decompose at 25–35°C.[16,17,18] Acyclic acetals give insufficient protection to allow preparation of Grignard reagents.[18]The protection of the ketone with 1,3-propanediol is not readily driven to completion, but with neopentanediol the equilibrium lies further toward ketal formation,[2] giving a better yield of more stable ketal.

β-Haloacetals and ketals have recently seen wide use as alkylating agents[9,19,3,20,21] and in the preparation of Grignard reagents. The Grignard reagents have been alkylated,[22] acylated,[15,23] added to carbonyl groups,[24,17,25,26,27,28,29,30] and used in Michael additions.[31,32,33] One example also gives a useful Wittig reagent.[8] Subsequent reactions of these products generally require removal of the acetal and ketal groups to regenerate the carbonyl function. This is readily done with aqueous acid in most cases, but not when aldehydes were protected with 1,3-diols because of the high equilibrium stability of the corresponding dioxanes. This problem is readily overcome by first converting to the dimethyl acetal in methanol and then using aqueous acid hydrolysis, or by using other specialized methods.[8,1534,35]

References and Notes

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

ethanol (64-17-5)

potassium carbonate (584-08-7)

acetic acid (64-19-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

Acrolein (107-02-8)

sodium bicarbonate (144-55-8)

hydrogen bromide, HBr (10035-10-6)

1,3-propanediol (504-63-2)

nitrogen (7727-37-9)

acetone (67-64-1)

toluene (108-88-3)

ethylene glycol (107-21-1)

ethylene (9002-88-4)

Ethyl orthoformate

triethyl orthoformate (122-51-0)

cinnamaldehyde

dichloromethane (75-09-2)

heptane (142-82-5)

crotonaldehyde (123-73-9)

methyl vinyl ketone (78-94-4)

2-(2-Bromoethyl)-1,3-dioxane (33884-43-4)

2,5,5-Trimethyl-2-(2-bromoethyl)-1,3-dioxane (87842-52-2)

dicinnamalacetone,
1,9-diphenylnona-1,3,6,8-tetraen-5-one (622-21-9)

neopentanediol

3-bromopropanal

4-bromo-2-butanone

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