Organic Syntheses

A Publication
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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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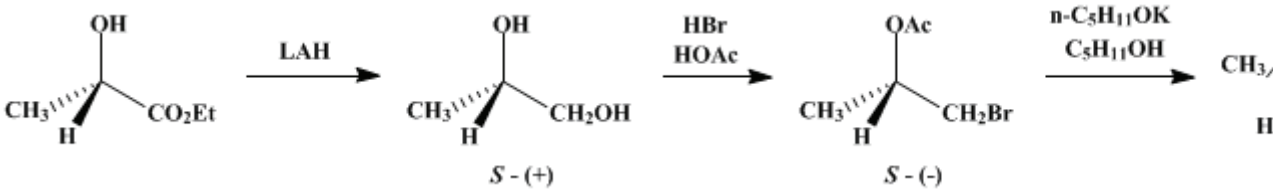
OPTICALLY ACTIVE EPOXIDES FROM VICINAL DIOLS VIA VICINAL ACETOXY BROMIDES: (*S*)-(−)- and (*R*)-(+)-METHYLOXIRANE



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Checked by Stephen H. Montgomery and Clayton H. Heathcock.

1. Procedure

A. *(S)-(+)-Propane-1,2-diol*. Into a three-necked, 500-mL, round-bottomed flask fitted with a mechanical stirrer, dropping funnel and reflux condenser are placed 10.8 g (0.284 mol) of lithium aluminum hydride and 200 mL of dry ethyl ether. To this slurry is added, from the dropping funnel, 33 g (0.28 mol) of ethyl L-(−)-lactate (Note 1) in 150 mL of dry ethyl ether at a rate that maintains a steady reflux. The heterogeneous mixture is stirred for 3 hr. Then 25 mL (1.39 mol) of water is carefully added and stirring is continued for a further 1.5 hr. The mixture is filtered and the white solid (LiOH) is washed well with ether and dichloromethane. The organic phases are combined, dried over magnesium sulfate, and concentrated at reduced pressure with a rotary evaporator to give a portion of the crude product (3 g). Aqueous 1 *M* sulfuric acid is added to the solid until the milky suspension is just acidic (pH 6–6.5). The suspension is subjected to continuous extraction with twice its volume of dichloromethane (about 500 mL) for 168 hr. The dichloromethane layer is dried over magnesium sulfate and concentrated at reduced pressure with a rotary evaporator. The crude products are combined and distilled at reduced pressure to obtain 14.4–15.6 g (68–73%) of (*S*)-(+)-propane-1,2-diol, bp 52–56°C (0.5 mm), as a colorless liquid (Note 2).

B. *(S)-(−)-2-Acetoxy-1-bromopropane*. A three-necked, 100-mL, round-bottomed flask fitted with a magnetic stirring bar, dropping funnel, and reflux condenser is charged with 7.6 g (0.1 mol) of (*S*)-(+)-propane-1,2-diol. A solution of 45% w/v hydrogen bromide–acetic acid (71 g, 0.3 mol) (Note 3) is added from the dropping funnel with cooling over ca. 5 min. The homogeneous solution is stirred at room temperature for 45 min, after which time it is added to 200 mL of water and the mixture neutralized immediately with solid sodium carbonate (Note 4). The neutral solution is extracted three times with 150 mL of ethyl ether, the organic phases are combined, dried over magnesium sulfate, and concentrated at reduced pressure with a rotary evaporator. Distillation of the crude product at reduced pressure affords 14.1–15.4 g (78–85%) of (*S*)-(−)-2-acetoxy-1-bromopropane, bp 54–57°C (7 mm), as a colorless liquid (Note 5).

C. *(S)-(−)-Methyloxirane*. To a three-necked, 100-mL, round-bottomed flask equipped with a magnetic stirring bar, pressure-equalizing dropping funnel, and 10-cm Vigreux column connected to an efficiently cooled condenser and receiver are added 9.05 g (50 mmol) of the acetoxybromopropane and 20 mL of dry 1-pentanol. The solution is stirred at room temperature and 41.66 mL (50 mmol) of 1.2 *M* potassium pentoxide in 1-pentanol (Note 6) is added from the dropping funnel over ca. 20 min. A white precipitate of potassium bromide is observed. After addition is complete, the flask is warmed in an oil bath at ca. 130–145°C to attain distillation (Note 7). The product, (*S*)-(−)-methyloxirane, 2.0–2.35 g (69–81%), is collected as a colorless liquid, bp 34–35°C (Note 8).

2. Notes

1. Ethyl L-(−)-lactate was purchased from Fluka AG, Buchs, Switzerland and was used directly.

Checkers found that fresh ethyl lactate purchased from Fluka is only 97–98% e.e. by ^{19}F NMR spectroscopy on the Mosher ester.

2. An optical rotation of $[\alpha]_D^{16}$ +20.3 (H_2O, *c* 7.5), [lit.[2] $[\alpha]_D^{20}$ +20.7° (H_2O, *c* 7.5))] was observed for this product. It had the following spectral properties: IR (liquid film, polystyrene reference) cm^{-1}: 3350 (s), 2970 (m), 2930 (m), 2870 (m), 1455 (m), 1375 (m); ^1H NMR ($CDCl_3$) δ: 1.15 (d, 3 H, -CH_3), 3.40 [q, 1 H, H_2C(OH)-] and 3.59 [q, 1 H, H_2C(OH)-], 3.89 [m, 1 H, -CH(OH) CH_3], -OH resonances variable.

3. Hydrogen bromide–acetic acid, 45%, was purchased from BDH Chemicals Ltd., Poole, England. The checkers used hydrobromic acid (30–32% in acetic acid, 4.1 *M*) from Fisher Scientific, 711 Forbes Ave., Pittsburgh, PA 51219.

4. Approximately 80 g of sodium carbonate is required. On addition of solid sodium carbonate a considerable amount of frothing occurs. To prevent the loss of product, the addition of the reaction mixture to the water and subsequent neutralization with solid sodium carbonate is performed in a 2-L beaker.

5. An optical rotation of $[\delta]_D^{20}$ −13.7° ($CHCl_3$, *c* 5.8), [lit.[2] $[\alpha]_D^{23}$ −13.55 ($CHCl_3$, *c* 5.8)] was observed for (*S*)-(−)-2-acetoxy-1-bromopropane. (*R*)-(+)-2-Acetoxy-1-bromopropane, obtained from (*R*)-(−)-propane-1,2-diol,[3,4] gave an optical rotation of $[\alpha]_D^{18}$ +14.1° ($CHCl_3$, *c* 5.8). Both enantiomers of acetoxybromopropane had the following spectral properties: IR (liquid film, polystyrene ref.) cm^{-1}: 2980 (w), 2937 (w), 1735 (s), 1450 (w), 1425 (w), and 1370 (s); ^1H NMR (CCl_4) δ: 1.34 (d, 3 H, CH_3), 2.10 (s, 3 H, -$OCOCH_3$), 3.38 (d, 2 H, -CH_2Br), and 4.97 [m, 1 H, -$CH(OCOCH_3)CH_3$] due to 2-acetoxy-1-bromopropane (94% by integration) and 1.70 (3 H) and 4.16 (3 H) due to 1-acetoxy-2-bromopropane (6%).

6. Potassium pentoxide in 1-pentanol is prepared by dissolving freshly cut potassium in dry, freshly distilled 1-pentanol under nitrogen. The molarity of this solution may be determined by titration against standard aqueous acid.

7. The oil bath is preheated to 120–130°C. It is then transferred to a prewarmed heater with stirrer on a lab jack below the reaction flask. The oil bath can then be moved into position with the aid of the lab jack.

8. An optical rotation of $[\alpha]_D^{20}$ −18.7° (CCl_4, *c* 5.83), [lit.[2] $[\alpha]_D^{22}$ −18.55° (CCl_4, *c* 5.84)] was observed for (*S*)-(−)-methyloxirane. (*R*)-(+)-Methyloxirane, obtained from (*R*)-(+)-acetoxybromopropane (Note 5), gave an optical rotation of $[\alpha]_D^{18}$ +19.13° (CCl_4, *c* 5.66), [lit.[2] $[\alpha]_D^{18}$ +18.7° (CCl_4, *c* 5.83)], bp 34–35°C, and a range of yields within the limits of those obtained for (*S*)-(−)-methyloxirane. Both enantiomers of methyloxirane had the following spectral properties; ^1H NMR (CCl_4) δ: 1.27 (d, 3 H, -CH_3), 2.27 (q, 1 H, -$CH(O)CH_2$), 2.59 [t, 1 H, -$CH(O)CH_2$] and 2.83 [m, 1 H, H_3C-$CH(O)CH_3$] ppm.

3. Discussion

This procedure illustrates the stereospecific conversion of 1,2-diols into vicinal acetoxy bromides by hydrogen bromide in acetic acid.[2] The acetoxy bromides that are formed are easily transformed into epoxides by base treatment. In the examples presented, the base is used in a high-boiling solvent to facilitate isolation of epoxide by direct distillation from the reaction mixture (see also [5,6,7,8]). For other examples, a solvent may be used that is either more volatile than the epoxide (e.g., methanol[2]) or easily removed by aqueous workup and solvent extraction of the epoxide (e.g., ethane-1,2-diol[9]). The hydrogen bromide–acetic acid method is superior to the preparation of epoxides from 1,2-diols via 1-*O*-sulfonate esters, because any contaminating 2-*O*-sulfonate ester will detract from the optical purity of the epoxide.[10] The optical purities of the samples of (*R*)- and (*S*)-methyloxirane prepared as described were better than 98%, according to complexation chromatography and ^1H NMR analysis with chiral shift reagent.[11,12] Other procedures for preparing (*R*)-[13,14] and (*S*)-methyloxirane have been described.[15,16,17] These compounds are valuable starting materials for preparing a variety of optically active natural products (nonactin,[18] sulcatol,[19] recifeiolide,[20] methyl-1,6-dioxaspiro[4.5]decanes[21]), drugs (e.g., *N*-2-hydroxypropyl-6,7-benzomorphans[22]) and for studies of stereoregular polymerizations.[23]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 434

References and Notes

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

H_2O

(LiOH)

Potassium pentoxide in 1-pentanol

nonactin

sulcatol

recifeiolide

N-2-hydroxypropyl-6,7-benzomorphan

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

methanol (67-56-1)

ether,
ethyl ether (60-29-7)

HYDROBROMIC ACID,
hydrogen bromide (10035-10-6)

sodium carbonate (497-19-8)

methyloxirane,
(75-56-9)

nitrogen (7727-37-9)

ethane-1,2-diol (107-21-1)

potassium bromide (7758-02-3)

potassium (7440-09-7)

dichloromethane (75-09-2)

ethyl lactate,
(687-47-8)

1-pentanol (71-41-0)

(57-55-6)

magnesium sulfate (7487-88-9)

lithium aluminum hydride (16853-85-3)

acetoxybromopropane,
(R)-(+)-acetoxybromopropane

potassium pentoxide

(R)-Methyloxirane,
(R)-(+)-Methyloxirane (15448-47-2)

(S)-(+)-Propane-1,2-diol (4254-15-3)

(R)-(+)-2-Acetoxy-1-bromopropane

(S)-methyloxirane (16088-62-3)

methyl-1,6-dioxaspiro[4.5]decane