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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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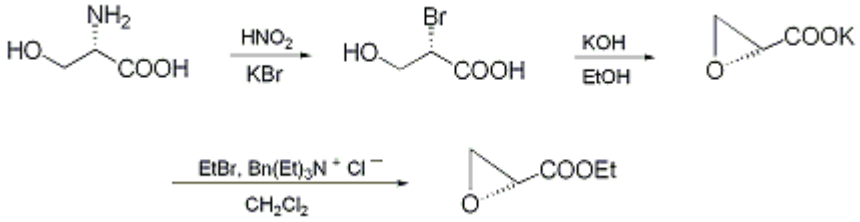
ETHYL GLYCIDATE FROM (S)-SERINE: ETHYL (R)-(+)-2,3-EPOXYPROPANOATE

[Oxiranecarboxylic acid, ethyl ester, (R)-]



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1. Procedure

(S)-(−)-2-Bromo-3-hydroxypropanoic acid . L-Serine (Note 1) (52.5 g, 0.5 mol) and potassium bromide, KBr, (200 g, 1.7 mol) (Note 2) are dissolved in water (400 mL). Hydrobromic acid (48%,123 mL, 1.09 mol) is added at room temperature and the mixture is cooled to −13°C with stirring (Note 3). Nitrogen, N_2, is bubbled through the solution and sodium nitrite (42.8 g, 0.62 mol) is slowly added in small portions (ca. 5 g every 15 min) (Note 4). After each addition, the reaction mixture turns brown and then the color slowly fades, but the solution does not decolorize entirely. The total time required for addition of all the sodium nitrite is approximately 2.5 hr. The solution is then allowed to warm to 0°C, the N_2 purge is stopped, and the mixture is stirred for 6 hr. Excess nitrogen oxides are removed by bubbling N_2 through the solution for 1 hr. The pale green solution is then extracted with ether (6 × 300 mL). The combined organic extracts are concentrated to 0.5 L by rotary evaporation and dried over anhydrous magnesium sulfate . After filtration, the ether is evaporated and the residual solvent is removed under reduced pressure (0.1 mm). The pale yellow or green oil (74-75 g, 87-89%) is used immediately in the next reaction without purification (Note 5), (Note 6), (Note 7).

Potassium (R)-(+)-2,3-epoxypropanoate (Potassium glycidate). The crude acid from the preceding step (74.5 g, 0.44 mol) is dissolved in absolute ethanol (300 mL) and cooled to −20°C. Under N_2, a filtered solution of potassium hydroxide (86%, 55.5 g, 0.85 mol) in absolute ethanol (300 mL) is slowly added. After 2 hr, the mixture is allowed to warm to 0°C and stirred at this temperature for 14 hr. The solution is filtered to remove precipitated salts. Half of the solvent is removed by rotary evaporation without warming and an additional crop of salt (2-4 g) is isolated by filtration. The combined salts are dried under vacuum to give 105 g of a 1 : 1 mixture of KBr and potassium glycidate .

One third of this mixture (35 g) is extracted by refluxing in a mixture of 585 mL of absolute ethanol and 15 mL of water in a 1-L flask with good stirring for 45 min (Note 8). After filtration of the hot suspension, the glycidate crystallizes from the filtered solution to give 12-13 g of product. Another third of the 1 : 1 KBr-potassium glycidate mixture is heated at reflux with stirring in the mother liquors for 45 min. After the second batch of crystalline potassium glycidate is isolated by filtration, the procedure is repeated with the last portion of the KBr-glycidate mixture. The solids collected from the three hot filtrations are combined and extracted a fourth time with the same solution, then crystallized to give additional product. After drying, the total weight of recrystallized potassium glycidate is 47-50 g. This salt contains 9.5-13% of KBr , and the yield is thus 74-80% (corrected for KBr content) (Note 9), (Note 10).

Ethyl (R)-(+)-2,3-epoxypropanoate (Ethyl glycidate). A suspension of dry potassium glycidate (26 g of an 90.5:9.5 potassium glycidate:KBr mixture, 0.186 mol), benzyltriethylammonium chloride (42.4 g, 0.186 mol), and ethyl bromide (76 g, 0.7 mol) in methylene chloride, CH_2Cl_2, (300 mL) is heated at reflux for 16 hr with good stirring (Note 11). The solvent and excess ethyl bromide are then slowly

removed by rotary evaporation without warming, and the resulting viscous solid is triturated with anhydrous diethyl ether (3 × 100 mL) to extract the ethyl glycidate . The combined ethereal extracts are filtered and dried over anhydrous magnesium sulfate. The solvent is slowly removed by rotary evaporation (without warming) and the residue is distilled at 40°C (2.4 mm) with 0°C water circulated through the condenser to afford 17.6 g of ethyl glycidate (81%) (Note 12), (Note 13).

2. Notes

1. L- or D-Serine are available from chemical suppliers such as Aldrich Chemical Company, Inc., Fisher Scientific Company, Fluka Chemical Corp., Acros Organics . In Europe, they may be obtained in bulk quantities from Degussa (Germany) and Rexim (France).
2. The excess of potassium bromide allows the required reaction temperature to be achieved; moreover, a high concentration of bromide ion suppresses the formation of the corresponding α-hydroxy acid.
3. An ice-sodium chloride mixture is used.
4. The exhaust gas is very acidic (pH ≤ 1 using wet pH paper), and therefore should be scrubbed by bubbling through a solution of potassium hydroxide.
5. The checkers obtained 74.5-78 g (88-92% yield) of product with $[\alpha]_D^{20}$ −10.2° (MeOH , *c* 5.1).
6. (S)-(−)-2-Bromo-3-hydroxypropanoic acid was characterized as follows: $[\alpha]_D^{20}$ −12.8° (MeOH, *c* 5.6); ^{1}H NMR (400 MHz, D_2O) δ: 3.76 (d, 2 H, J = 6.0), 4.29 (t, 1 H, J = 6.0) ; ^{13}C NMR (100 MHz, d_6-acetone) δ: 46.1, 64.2, 170.1 ; IR (neat) cm^{-1}: 3400-3000, 2960, 2660, 1735, 1465, 1410, 1260, 1200, 1170, 1080, 1040, 945, 850 ; MS m/z 169 (M+H) ; HRMS (CI, CH_4) for $C_3H_6BrO_3$ [M+H] calcd 168.9500, found 168.9499; Anal. Calcd for $C_3H_5BrO_3$: C, 21.33; H, 2.98. Found: C, 21.66; H, 2.92.
7. The checkers found that the product partially decomposed when stored for a day at ambient temperature. Therefore it is recommended that the bromo acid be used immediately in the next step.
8. The success of this extraction is highly dependent on the efficiency of the stirring; best results are obtained with a good magnetic stirrer at 1200 rpm using an egg-shaped magnetic stir bar (40 × 13 mm).
9. The amount of potassium bromide remaining in the recrystallized potassium glycidate is determined by potentiometric titration using a silver electrode.
10. An analytical sample was generated by an additional recrystallization from EtOH : mp 180°C (dec); $[\alpha]_D^{20}$ +32.1° (H_2O, *c* 20); ^{1}H NMR (400 MHz, D_2O) δ: 2.64-2.66 (m, 1 H), 2.79-2.82 (m, 1 H), 3.22-3.24 (m, 1 H) ; ^{13}C NMR (100 MHz, d_6-DMSO/D_2O) δ: 46.0, 50.3, 174.7 ; IR (KBr) cm^{-1}: 1620 (br), 1440, 1240, 915, 860, 820, 770, 680 .
11. A 50°C oil bath was used to maintain gentle reflux.
12. The purity of the ethyl glycidate prepared according to this procedure was ≥97% as measured by gas chromatography (BP5 capillary column from SGE). The enantiomeric purity was greater than 99% ee as determined by chiral gas chromatography on a 50-m CYDEX-B capillary column (β-cyclodextrin stationary phase) from SGE: bp 68-69°C (15 mm); bp 40°C (2.4 mm); $[\alpha]_D^{20}$ +15.8° (neat); $[\alpha]_D^{20}$ +12.3° (MeOH, *c* 5.0); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.24 (t, 3 H, J = 7.2), 2.87 (A of ABX, 1 H, J_{AB} = 6.6, $J_{A,X}$ = 4.2), 2.89 (B of ABX, 1 H, J_{AB} = 6.6, J_{BX} = 2.4), 3.36 (X of ABX, 1 H, J_{AX} = 4.2, J_{BX} = 2.4), 4.16 (B of AB as q, 1 H, J_{BA} = 10.8, $J_{B,Me}$ = 7.2), 4.19 (A of AB as q, 1 H, J_{AB} = 10.8, $J_{A,Me}$ = 7.2) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 46.1, 47.2, 61.5, 169.1 ; IR (neat) cm^{-1}: 2995, 1752, 1417, 1392, 1298, 1260, 1211, 1040, 922, 866, 760 ; MS m/z 117 (M+H) ; HRMS (CI, CH_4) for $C_5H_9O_3$ [M+H] calcd 117.0552, found 117.0551. Anal. Calcd for $C_5H_8O_3$: C, 51.72; H, 6.94. Found: C, 51.59; H, 6.90.
13. Ethyl glycidate is a rather sensitive compound (it cannot be chromatographed on silica gel) and distillation at low temperature under high vacuum (0.1-2 mm) avoids the formation of undistillable residues resulting from polymerization. The product should be stored at 5°C (or lower) and is perfectly stable at this temperature.

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

This procedure describes an efficient method for the synthesis of ≥99% enantiomerically pure ethyl glycidate from L-serine. Although preparation of potassium glycidate via cyclization of 3-bromo-2-

hydroxypropionic acid ,[2] and from 3-chloro-2-hydroxypropionic acid (obtained by microbial reduction of chloropyruvic acid)[3] was previously reported, the corresponding ethyl ester was never described. An enantioselective synthesis of the 2,3-epoxy acid by oxidation of 2,3-epoxypropanol has also been reported.[4]

Ethyl 2,3-epoxypropanoate is a very interesting chiron. It may be opened by various organometallic compounds such as dialkyl, diaryl, and divinyl lithium cuprates, dialkylmagnesium cuprates, trialkylalanes and aluminum acetylides.[5,6] The epoxide ring is attacked regiospecifically at the β-position and produces α-hydroxy esters exclusively without racemization. The same result is observed with heteronucleophiles such as azide anion. However, thiolates afford a mixture of α and β opening.

After protection, the α-hydroxy esters can be reduced by DIBAL-H into O-protected α-hydroxyaldehydes that are very useful synthetic intermediates (e.g., leukotrienes,[7,8,9] ionophore antibiotics,[10] insect pheremones,[11] etc.). The secondary hydroxyl group of the α-hydroxy esters may also be substituted with inversion of configuration after activation as triflates of nosylates (p-nitrobenzenesulfonates) to give α-alkyl esters[12] or α-amino esters.[13]

Methyl 2,3-epoxypropanoate can be prepared by reaction of potassium glycidate with dimethyl sulfate and one equivalent of benzyltriethylammonium chloride in methylene chloride at room temperature (65% yield).[14] The reactions of this ester with organolithium or organomagnesium reagents at low temperature afford optically pure epoxy ketones[14] that may be transformed via reductive amination to anti amino epoxides.[15]

Using benzyl bromide as the alkylation agent, the corresponding benzyl glycidate is obtained in 60% yield.[5,16] In contrast with ethyl glycidate, this compound is not stable to distillation; however, it can be purified by chromatography on silica gel.

The preparation of cis-methyl or ethyl 2,3-epoxybutanoate from threonine can also be accomplished using the procedure described here.[17] This latter was used in the stereocontrolled synthesis of codonopsinine.[18]

References and Notes

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

Ethyl glycidate:
Oxiranecarboxylic acid, ethyl ester, (R)- (12); (111058-33-4)

(S)-Serine:
L-Serine (8,9); (56-45-1)

(S)-(−)-2-Bromo-3-hydroxypropanoic acid:
Propanoic acid, 2-bromo-3-hydroxy-, (S)- (10); (70671-46-4)

Potassium bromide (8,9); (7758-02-3)

Hydrobromic acid (8,9); (10035-10-6)

Sodium nitrite:
Nitrous acid, sodium salt (8,9); (7632-00-0)

Potassium (R)-(+)-2.3-epoxypropanoate:
Oxiranecarboxylic acid, potassium salt, (R)-(11); (82044-23-3)

Benzyltriethylammonium chloride:
Ammonium, benzyltriethyl-, chloride (8);
Benzenemethanaminium, N,N,N-triethyl-, chloride (9); (56-37-1)