A short synthesis of 4-amino-3-hydroxybutyric acid (GABOB) *via* allyl cyanide

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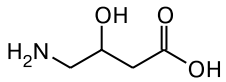
4-Amino-3-hydroxybutyric acid was synthesized from allyl cyanide in four steps in an overall yield of 38%. Ultrasonically promoted epoxidation of allyl cyanide with *m*-chloroperoxybenzoic acid giving oxiranylacetonitrile was used as a key step.

Key words: 4-amino-3-hydroxybutyric acid, GABOB, allyl cyanide, epoxidation, sonification, azides.

4-Amino-3-hydroxybutyric acid (GABOB) is a compound having neuromodulator,[1] antiepileptic,[2] and hypotensive[3] activity. Therefore, it is classified as an anticonvulsant[4] drug. It has two enantiomeric forms (R)-GABOB and (S)-GABOB, each involved in 4-aminobutyric acid (GABA) transport processes.[5] Carnitine[6] available from the methylation of GABOB plays a key role in the transportation of fatty acids through the mitochondrial membranes.



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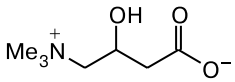

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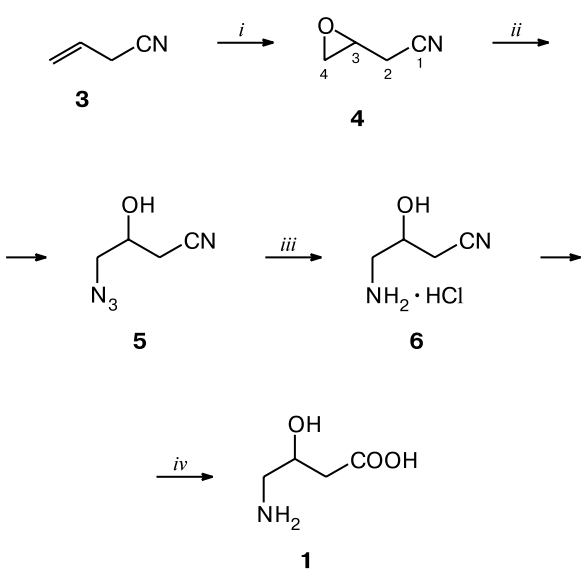
To date, over 20 synthetic procedures have been described for (*R*,*S*)-GABOB in the literature. For this purpose, 2-(4-chloro-2-hydroxybutyl)isoindole-1,3-dione,[7] phthaloyl glycine,[8] 4-aminobutyric acid,[9] epichlorohydrin[10], 4-halo-3-oxobutyric acid anilides,[11] crotonic acid,[12] 4-chloro-3-hydroxybutyric acid methyl ester[13], and 4-hydroxypyrrolidin-2-one[14] have been used as starting materials. Over 40 methods for (*R*)-GABOB [15] and about 20 for (*S*)-GABOB [16] have been developed. In this study we present a method for the convenient synthesis of (*R*,*S*)-GABOB starting from allyl cyanide.

Our synthesis is outlined in Scheme 1. The first step is the epoxidation of the double bond of allyl cyanide (**3**). As this olefin is monosubstituted, its reaction with *m*-chloroperoxybenzoic acid (MCPBA) occurs too slowly.[17] In order to expedite the reaction, we ultrasonically irradiated the reaction medium. The ultrasonicated epoxidation of allyl cyanide (**3**) using 1 equiv. MCPBA gave epoxide **4** in a yield of 61%. Attempts to directly substitute epoxide **4** with NH_3 to give 4-amino-3-hydroxybutyronitrile failed. The NH_4Cl catalyzed substitution of epoxide **4** with NaN_3 afforded 4-azido-3-hydroxybutyronitrile (**5**) in a yield of 85%. The Pd/C-catalyzed hydrogenation of azide **5** in the presence of $CHCl_3$ afforded 4-amino-3-hydroxybutyronitrile hydrochloride (**6**) in a yield of 96%. Acidic hydrolysis of nitrile **6** gave (*R*,*S*)-4-amino-3-hydroxybutyric acid (**1**) in a yield of 75%.

Scheme 1



Reagents and conditions. *i*. MCPBA, $CHCl_3$, ultrasonic bath, 20 °C, 48 h, 61% yield; *ii*. NaN_3, NH_4Cl, 80% EtOH (aq.), 20 °C, 24 h, 85% yield; *iii*. H_2 (1 atm), Pd/C, $CHCl_3$, EtOH, 24 h, 96% yield; *iv*. H_2SO_4, H_2O; then $BaCO_3$ and Amberlite IR-120, 75% yield.

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Thus, we described a method for the easy and convenient synthesis of (*R*,*S*)-GABOB *via* allyl cyanide, a commercially available and cheap starting material, in four steps, giving an overall yield of 38%.

Experimental

Melting points were determined on a Büchi 530 instrument and were not corrected. IR spectra were recorded on a Mattson 1000 FT-IR spectrophotometer in KBr pellets or in thin layer. ^{1}H and ^{13}C NMR spectra were obtained on a Varian spectrometer (working frequency 200 and 50 MHz for ^{1}H and ^{13}C, respectively).

Caution! Allyl cyanide may be harmful if absorbed through the skin. It may cause eye and skin irritation. It may also cause respiratory and digestive tract irritation. Therefore, a fume hood should be used during experiments and gloves should be worn.

2-Oxiranylacetonitrile (4). MCPBA (44.13 g, 70%, 179 mmol) was added to a solution of allyl cyanide **3** (12 g, 179 mmol) in $CHCl_3$ (140 mL). The resulting solution was sonicated in an ultrasonic bath (47 kHz) for two days. A saturated aqueous solution of $NaHSO_3$ (100 mL) was added to reduce unreacted MCPBA. The organic phase was separated, washed with saturated aqueous $NaHCO_3$ (2×50 mL), and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave epoxynitrile **4** [17] as a colorless oil (9.07 g, 61%). ^{1}H NMR ($CDCl_3$), δ: 3.15—3.07 (m, 1 H, H(3)); 2.77 (t, 1 H, H_a(4), J = 4.3 Hz); 2.70—2.56 (m, 3 H, H_b(4), H_a(2), H_b(2)). ^{13}C NMR ($CDCl_3$), δ: 115.3 (C(1)), 46.3 (C(3) or C(4)), 45.7 (C(4) or C(3)), 20.7 (C(2)). IR (KBr), ν/cm^{-1}: 2249 (CN).

4-Azido-3-hydroxybutyronitrile (5). NaN_3 (2.90 g, 44.6 mmol) and NH_4Cl (2.40 g, 44.8 mmol) were added to a solution of 2-oxiranylacetonitrile **4** (3.00 g, 36.1 mmol) in 80% aqueous EtOH (50 mL). The resulting mixture was refluxed for 24 h. The reaction mixture was poured into water (100 mL). The organic phase was extracted with Et_2O (2×50 mL), dried ($MgSO_4$), and evaporated to give 4-azido-3-hydroxybutyronitrile **5** [18] as a yellow oil (3.87 g, 85%). 4-Azido-3-hydroxybutyronitrile **(5)** had at least 95% purity (^{1}H NMR) and was used without further purification in the next reaction. ^{1}H NMR ($CDCl_3$), δ: 4.19—4.03 (sextet, after exchange with D_2O quintet, 1 H, H(3), J = 5.5 Hz); 3.67 (d, 1 H, OH, J = 5.3 Hz); 3.41 (d, 2 H, C(4)H_2, J = 5.1 Hz); 2.65 (d, 2 H, C(2)H_2, J = 5.9 Hz). ^{13}C NMR ($CDCl_3$), δ: 116.9 (C(1)), 66.5 (C(3)), 55.1 (C(4)), 23.1 (C(2)). IR (KBr), ν/cm^{-1}: 3438 (OH), 2289 (CN), 2136 (N_3).

4-Amino-3-hydroxybutyronitrile hydrochloride (6) was prepared by hydrogenation of the respective azide by a modified procedure.[18] Into a 100-mL flask were placed Pd/C (50 mg) and 4-azido-3-hydroxybutyronitrile (**5**) (2.40 g, 19 mmol) in EtOH (50 mL) and $CHCl_3$ (0.5 mL). A balloon filled with H_2 gas (3 L) was attached to the flask. The reaction mixture was hydrogenated for 24 h at 20 °C and under normal pressure. The catalyst was removed by filtration. The filtrate was concentrated to give 4-amino-3-hydroxybutyronitrile hydrochloride (**6**) [18] as a light brown oil (2.50 g, 96%). ^{1}H NMR (D_2O), δ: 4.24—4.15 (m, 1 H, H(3)); 3.25—2.95 (m, 2 H, C(4)H_2); 2.92—2.64 (m, 2 H, C(2)H_2). ^{13}C NMR (D_2O), δ: 123.3 (C(1)), 68.3 (C(3)), 48.4 (C(4)), 28.4 (C(2)). IR (KBr), ν/cm^{-1}: 3500—2900, 2261, 1612, 1510, 1458, 1413, 1041. The ^{1}H NMR and IR data are in agreement with the data given in the literature.[18]

4-Amino-3-hydroxybutyric acid (1). Amine hydrochloride **6** (2.20 g, 16 mmol) was dissolved in 98% H_2SO_4 (2 mL, 38 mmol) and heated for 5 min. Then it was diluted with 20 mL of water and heated to reflux for 3 h. After being cooled, the solution was made basic with excess $BaCO_3$ and heated for 1 h. Then it was filtered with suction and exactly neutralized with several drops of 2% H_2SO_4. The water was evaporated, and the resulting mixture was filtered through Amberlite IR-120 (H^+) eluting with a 10% NH_3 solution. The eluate was concentrated to give 4-amino-3-hydroxybutyric acid (**1**) (1.44 g, 75%) as a white solid, m.p. 214—215°C (recrystallized from an EtOH—water mixture; *cf.* Ref. 7a: m.p. 214 °C). ^{1}H NMR (D_2O), δ: 4.10 (m, 1 H, H(3)); 3.07 (dd, A part of ABX system, 1 H, H_a(4), ^3J = 3.2 Hz, ^2J = 13.1 Hz); 2.85 (dd, B part of ABX system, 1 H, H_b(4), ^3J = 9.4 Hz, ^2J = 13.1 Hz); 2.35 (d, 2 H, C(2)H_2, J = 6.8 Hz). ^{13}C NMR (D_2O), δ: 183.1 (C(1)), 70.1 (C(3)), 48.8 (C(4)), 46.8 (C(2)). IR (KBr), ν/cm^{-1}: 3444, 3066—2576, 2132, 1631, 1562, 1407, 1265, 1118, 1064, 1022, 975. The ^{1}H NMR, ^{13}C NMR, and IR data are in agreement with the data given in the literature.[19]

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