Facile Synthesis of Optically Active Homocysteine from Methionine

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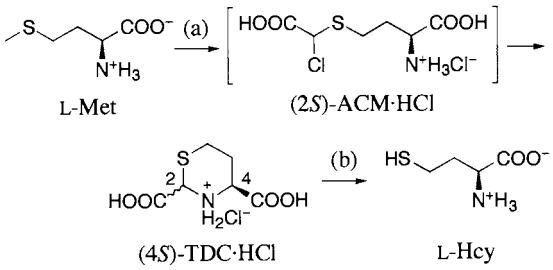
L-Methionine (L-Met) reacted with dichloroacetic acid in concentrated hydrochloric acid under refluxing to give (4*S*)-1,3-thiazane-2,4-dicarboxylic acid hydrochloride [(4*S*)-TDC·HCl]. L-Homocysteine (L-Hcy) was obtained in an optically pure form by treatment of (4*S*)-TDC·HCl with hydroxylamine hydrochloride. D-Hcy was also synthesized starting from D-Met via (4*R*)-TDC·HCl intermediate.

L- And D-homocysteines (L- and D-Hcy), non-proteinogenic α-amino acids, are useful as key intermediates for syntheses of pharmaceutical chemicals. For example, L-Hcy has been used as a chiral building block for syntheses of benzo-fused azepinone and piperidinone compounds, which are selective angiotensin-converting enzyme inhibitors.[1] Therefore, Hcy is required to be used as a single enantiomer. Hcy has been synthesized from methionine (Met) as derivatives, such as homocystine, which is reduced with sodium in liquid ammonia to Hcy, and homocysteine thiolactone, which generates Hcy under alkaline conditions. Although L-Met has been reported to afford homocystine by refluxing in sulfuric acid, the obtained homocystine undergoes partial racemization.[2] In addition, L-Met is refluxed in hydroiodic acid to give racemic homocysteine thiolactone hydroiodide.[3] Optically active Hcy is obtained via asymmetric transformation of (*RS*)-1,3-thiazane-4-carboxylic acid[4] and as *N*-acyl homocysteine thiolactone by optical resolution.[5] We designed a method to synthesize D- and L-Hcy in optically pure forms from optically active Met by a more facile procedure.

We attempted synthesis of a 1,3-thiazane derivative from Met because the derivative was easily ring-opened by treatment with hydroxylamine to give Hcy.[4] L-Met reacts with benzyl chloride and chloroacetic acid in concentrated hydrochloric acid under refluxing to afford *S*-benzyl-l-homocysteine[6] and (*S*)-2-amino-4-[(carboxymethyl)sulfanyl]butanoic acid,[7] respectively. Therefore, we first attempted to synthesize (2*S*)-2-amino-4-[(carboxychloromethyl)sulfanyl]butanoic acid hydrochloride [(2*S*)-ACM·HCl] by reacting L-Met with dichloroacetic acid in concentrated hydrochloric acid under refluxing and then to obtain (4*S*)-1,3-thiazane-2,4-dicarboxylic acid [(4*S*)-TDC], which seemed to be a precursor of L-Hcy, by intramolecular condensation of (2*S*)-ACM·HCl (Scheme 1).

After refluxing (105 °C) the mixture of L-Met (50.0 mmol, 7.46 g) and dichloroacetic acid (50.0–300 mmol) in concentrated hydrochloric acid (100 cm^3) for 6 h, followed by concentrating to 30 cm^3 *in vacuo* at 60 °C, the mixture was allowed to stand overnight at 5 °C. The precipitated compound was collected by filtration, washed thoroughly with tetrahydrofuran, and dried. The filtrate was evaporated to dryness *in vacuo* to give oily matter, and then ethanol (10 cm^3) was added to the residue. After allowing the mixture to stand overnight at 5 °C,



Scheme 1. Reagents and conditions: a) L-Met, dichloroacetic acid, conc. HCl, reflux; b) hydroxylamine hydrochloride, triethylamine.

further precipitate was collected by filtration. However, its elemental analysis and ^1H NMR spectrum indicated that the obtained compound was not (2*S*)-ACM·HCl.[8] The compound was determined to be (4*S*)-TDC hydrochloride [(4*S*)-TDC·HCl], because its ^1H and ^{13}C NMR and IR spectra were identical to those of (4*S*)-TDC·HCl, which was obtained by reacting L-Hcy with glyoxylic acid monohydrate.[8,9] Therefore, the (2*S*)-ACM·HCl that was formed by the reacting L-Met with dichloroacetic acid was estimated to immediately undergo intramolecular condensation to give (4*S*)-TDC·HCl. As shown in Figure 1, the reaction of L-Met (50.0 mmol) with dichloroacetic acid (200 mmol) afforded (4*S*)-TDC·HCl in the highest yield (40.7%). (4*S*)-TDC·HCl should be obtained as a mixture of two diastereoisomers because of formation of a chi-

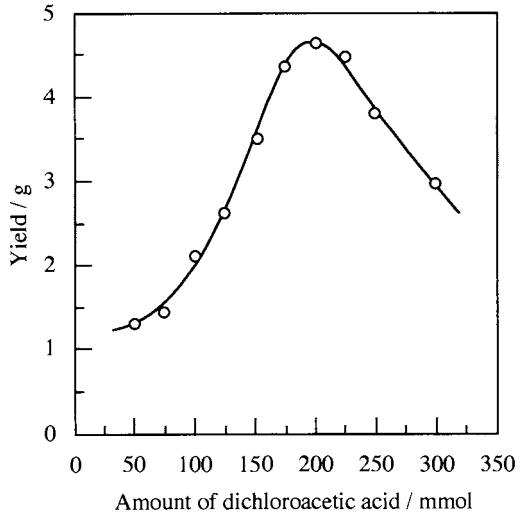


Figure 1. Synthesis of (4*S*)-1,3-thiazane-2,4-dicarboxylic acid hydrochloride. Conditions: L-Met, 50.0 mmol (7.46 g); dichloroacetic acid, 50.0–300 mmol; conc. HCl, 100 cm^3; the reaction mixture was refluxed (105 °C) for 6 h.

ral center at the C-2 position. In the ^{1}H NMR spectrum of (4*S*)-TDC·HCl, which was synthesized from L-Hcy, methine protons at the C-2 positions appeared at 5.39 and 5.23 ppm in the intensity ratio of 1:66.5 as singlet signals.[10] Therefore, the intensity ratio suggested that one of (4*S*)-TDC·HCl diastereomers was obtained in 97% de. On the other hand, the reaction of L-Met with dichloroacetic acid yielded (4*S*)-TDC·HCl as a single diastereoisomer because the obtained (4*S*)-TDC·HCl did not show any proton signals due to another diastereoisomer.

The obtained (4*S*)-TDC·HCl was treated with hydroxylamine hydrochloride without purification to give L-Hcy. Thus, a suspension of (4*S*)-TDC·HCl (20.0 mmol, 4.55 g) in 100 cm^3 of ethanol was adjusted with triethylamine to pH 7; (4*S*)-TDC·HCl was completely dissolved in ethanol. To the solution was gradually added 40 cm^3 of 0.5 mol dm^{-3} ethanolic hydroxylamine hydrochloride at 10 min intervals (8 cm^3 × 5) under refluxing. After adding the ethanol solution of hydroxylamine hydrochloride (8 cm^3), the mixture was immediately maintained at pH 7 to 8 with triethylamine. After further refluxing the mixture for 1 h, followed by cooling to room temperature, the precipitated L-Hcy was collected by filtration, washed with methanol, and dried; the yield was 2.02 g (74.8%).[11] In addition, D-Hcy was synthesized from D-Met by the method similar to that described for L-Hcy; the yield was 2.00 g (74.1%).[12,13]

As described above, L- and D-Hcys were easily obtained in optically pure forms by synthesizing from L- and D-Mets via (4*S*)- and (4*R*)-TDC·HCl as the intermediates, respectively.

References and Notes

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8 The (4*S*)-TDC·HCl obtained by the reaction of L-Met (50.0 mmol) with dichloroacetic acid (200 mmol): Yield 4.63 g (40.6%); mp 178–179 °C (decomp); $[\alpha]_D^{20}$ +6.6° (*c* 1.00, water); IR (KBr) $\nu_{C=O}$ 1763, 1742 cm^{-1}; ^{1}H NMR (270 MHz, D_2O) δ = 5.23 (1H, s, -SC*H*(COOH)N$^+$H$_2$-), 4.11 (1H, dd, *J* = 2.8, 12.8 Hz, -H$_2$N$^+$C*H*(COOH)CH$_2$-), 3.26–3.15 (1H, m), 3.05–2.97 (1H, m), 2.73–2.64 (1H, m), 2.13–1.97 (1H, m); ^{13}C NMR (67.5 MHz, D_2O) δ = 152.9, 150.4, 41.4, 40.1, 9.5, 9.2. Found: C, 31.43; H, 4.25; N, 6.14%. Calcd for $C_6H_{10}ClNO_4S$: C, 31.65; H, 4.43; N, 6.15%.

9 L-Hcy was obtained via asymmetric transformation of (*RS*)-THA by using (2*R*,3*R*)-tartaric acid as the resolving agent and salicylaldehyde as the epimerization catalyst in propanoic acid; (*RS*)-THA was prepared from (*RS*)-homocysteine thiolactone hydrochloride. The obtained (*S*)-1,3-thiazane-4-carboxylic acid was treated with hydroxylamine hydrochloride in ethanol to give L-Hcy.[4]

10 (2*S*)-TDC·HCl from L-Hcy: Mp 181–183 °C (decomp); $[\alpha]_D^{20}$ +5.8° (*c* 1.00, water); ^{1}H NMR (270 MHz, D_2O) δ = 5.89 (s, -SC*H*(COOH)N$^+$H$_2$-), 5.23 (1H, s, -SC*H*(COOH)-N$^+$H$_2$-), 4.7–4.6 (m, -H$_2$N$^+$C*H*(COOH)CH$_2$-), 4.11 (1H, dd, *J* = 2.8, 12.8 Hz, -H$_2$N$^+$C*H*(COOH)CH$_2$-), 3.26–3.15 (1H, m), 3.05–2.97 (1H, m), 2.73–2.64 (1H, m), 2.6–2.5 (m), 2.3–2.4 (m), 2.13–1.97 (1H, m). The IR spectrum was idential to that of (2*S*)-TDC·HCl from L-Met.

11 L-Hcy: Mp 247–249 °C (decomp); $[\alpha]_D^{20}$ +27.2° (*c* 1.00, 1 mol dm^{-3} HCl) (ref.[4] $[\alpha]_D^{20}$ +26.8° (*c* 1.00, 1 mol dm^{-3} HCl)); IR (KBr) $\nu_{C=O}$ 1586 cm^{-1}; ^{1}H NMR (270 MHz, D_2O) δ = 3.89 (1H, dd, *J* = 5.9, 7.0 Hz, -C*H*(NH$_2$)COOH), 2.73–2.56 (2H, m, -C*H*$_2$SH), 2.25–2.07 (2H, m, -CH$_2$-); ^{13}C NMR (67.5 MHz, D_2O) δ = 176.7, 56.1, 37.2, 22.4. Found: C, 35.56; H, 6.41; N, 10.29%. Calcd for $C_4H_9NO_2S$: C, 35.54; H, 6.71; N, 10.36%.

12 (4*R*)-TDC·HCl: Yield 4.73 g (41.5%); mp 176–179 °C (decomp); $[\alpha]_D^{20}$ –6.5° (*c* 1.00, water). The ^{1}H and ^{13}C NMR and IR spectra were virtually identical to those of (4*S*)-TDC·HCl.

13 D-Hcy: Mp 248–250 °C (decomp); $[\alpha]_D^{20}$ –27.2° (*c* 1.00, 1 mol dm^{-3} HCl) (ref.[4] $[\alpha]_D^{20}$ –26.8° (*c* 1.00, 1 mol dm^{-3} HCl)). The ^{1}H and ^{13}C NMR and IR spectra were virtually identical to those of L-Hcy.