Stereospecific Synthesis of Azetidine-*cis*-2,3-dicarboxylic Acid

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Received September 19, 2002; accepted October 23, 2002

Electrocyclic reaction product of 1-(methoxycarbonyl)-1,2-dihydropyridine was stereospecifically converted by RuO_4 oxidation into azetidine-*cis*-2,3-dicarboxylic acid.

Key words azetidine-*cis*-2,3-dicarboxylic acid; 1,2-dihydropyridine; ruthenium tetroxide; 2-(methoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-ene

We have previously reported a study of the synthesis of amino acids using Diels–Alder (D–A) adducts of dienes and *N*-containing dienophiles.[1,2] Subsequently, our interests turned to the synthesis of additional amino acids from other *N*-containing olefins, which can be prepared by pericyclic reaction.

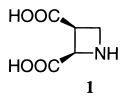
In the present paper, we would like to report the synthesis of azetidine-*cis*-2,3-dicarboxylic acid (**1**) using the electrocyclic reaction of 1,2-dihydropyridine followed by ruthenium tetroxide oxidation. Bridges *et al.* reported the first synthesis of azetidine-2,3-dicarboxylic acids; their inhibition activities against the high affinity L-glutamate transporter were examined, but the details of the synthetic procedure and the physical data of the compounds were not described.[3]

Bicyclic alkene **3**, which can be transformed to certain useful compounds,[4—11] is known to be easily prepared by a photoinduced electrocyclic reaction of 1-methoxy-1,2-dihydropyridine.[4—8] As variation among yields has been frequently observed, depending on the irradiation conditions,[12] compound **2** was exposed to UV rays using a high-pressure mercury lamp through a Pyrex filter, basically according to Fowler's method,[4] to give bicyclic alkene **3** in 85% yield. Oxidation of compound **3** by RuO_4 was achieved at 0 °C for 80 h, giving the corresponding dicarboxylic acid, which was treated with diazomethane and isolated as dimethyl ester **4** in a 58% yield. Attempts at the hydrolysis of **4** with hydrochloric acid were made, but both treatments with 6 M HCl at 50 °C for 6 d and with 4 M HCl at 95 °C for 2 d afforded complicated mixtures of products (Chart 1). As the failure of these hydrolyses was attributed on one hand to the difficulty of removing the *N*-methoxycarbonyl group and on the other hand to the ease of epimerization, we planned to exchange the *N*-methoxycarbonyl group for an *N*-*tert*-butoxycarbonyl (Boc) group.

Although removal of the methoxycarbonyl group from compound **3** by methyl lithium has been reported,[5,6] we newly executed a simple alkaline hydrolysis of **3** to achieve ease of handling. Compound **3** was heated with 2 M NaOH–EtOH under reflux for 24 h and the reaction mixture was treated with the ethereal solution of di-*tert*-butyl dicarbonate to give Boc form **5** in a 57% yield. The olefinic linkage of **5** was oxidized under similar conditions to those employed for the oxidation of **3**, but both the disappearance of **5** and the completeness of the expected reaction appeared to be faster than those of **3**. We concluded that the difference between the reaction rates was due to the solubilities of the intermediate products in AcOEt. The generated dicarboxylic acid was treated with diazomethane to give dimethyl ester **6** in a 67% yield (2 steps).

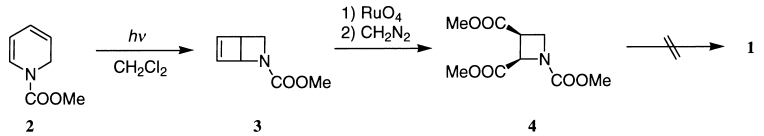
Compound **6** was heated with 6 M HCl–AcOH at 50 °C for 3 d and the salt of the target amino acid, which was obtained after concentration of the reaction mixture, and was desalted simply by dissolving the residue in hot water to give free amino acid **1** as colorless prisms in an 85% yield (Chart 2).

The stereochemistry of **1** was confirmed by observation of the coupling constants and the nuclear Overhauser effects (NOE) of the ^{1}H-NMR analysis (Fig. 2). The coupling constant between H^2 (δ 5.39) and H^3 (δ 3.94) was 9.9 Hz, that



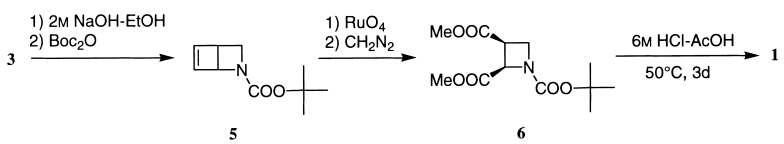
1

Fig. 1



2 **3** **4**

Chart 1



5 **6**

Chart 2

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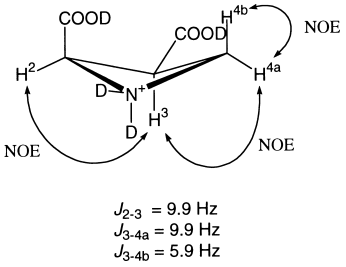

Fig. 2. Coupling Constants and NOE Relationships of the Target Amino Acid **1** in 1 M DCl

between H^3 and H^{4a} (δ 4.31) was 9.9 Hz, and that between H^3 and H^{4b} (δ 4.11) was 5.9 Hz. No NOE was observed between H^3 and H^{4b}, which implies that the relative configuration between 2- and 3-position is *cis*.

Thus, we accomplished the stereospecific synthesis of azetidine-*cis*-2,3-dicarboxylic acid (**1**).

Experimental

Melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. NMR spectra were recorded in chloroform-*d* ($CDCl_3$), except for those of the amino acid on a GSX-400 spectrometer with tetramethylsilane as an internal standard. For the amino acid, analysis was performed in 1 M deuterium chloride (DCl) with 1,4-dioxane as an internal standard (δ: 3.7 for ^{1}H-NMR and δ: 67.4 for ^{13}C-NMR). Infrared (IR) spectra were recorded on a Hitachi 270-30 spectrophotometer. Mass spectra (MS) were obtained with a JEOL JMS-DX300 instrument. Column chromatography was performed on silica gel (Kieselgel 60, 70—230 mesh, Merck) or alumina (Aluminium oxide 90, 70—230 mesh, Merck).

1-(Methoxycarbonyl)-1,2-dihydropyridine (2) This compound was prepared according to the cited method[4] with little modification. A solution of methyl chlorocarbonate (18.9 g, 0.200 mol) in ether (25 ml) was added to a mixture of sodium borohydride (8.00 g, 0.211 mol), pyridine (15.8 g, 0.200 mol), and MeOH (150 ml) cooled in Dry Ice-acetone. The rate of addition was controlled such that the temperature of the reaction mixture did not exceed −73 °C. The reaction mixture was stirred for an additional 1 h and was then poured into ice water (200 ml). After all of the ice melted, the mixture was extracted with ether (100 ml×4). The ether layer was washed with water (100 ml×4) and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave compound **2** (24.0 g), which was contaminated by small amounts of impurities, but was used for the next step without further purification. ^{1}H-NMR ($CDCl_3$) δ: 3.62 (3H, m, OCH_3), 4.15—4.32 (2H, m, CH_2), 4.88—4.98 (3H, m, 3-,4-,5-H), 6.57 (1H, d, J=7.5 Hz, 2-H).

Methyl 2-Azabicyclo[2.2.0]hex-5-ene-2-carboxylate (3) This compound was also prepared according to the cited method[4] with minor modification. A solution of **2** (10.0 g, 71.9 mmol) in dichloromethane (1500 ml) was irradiated using a high-pressure mercury lamp (Ushio UM452, 450W, Pyrex filter, under Ar) for 48 h. Removal of the solvent gave a yellow oil, which was subjected to column chromatography on alumina (ether) to give **3** (8.50 g, 85%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 3.67 (3H, m, OCH_3), 3.27—4.17 (3H, m, CH_2, 4-H), 4.73—4.93 (1H, m, 1-H), 6.43—6.63 (2H, m, olefinic H).

Trimethyl *cis*-Azetidine-1,2,3-tricarboxylate (4) A solution of **3** (500 mg, 3.59 mmol) in AcOEt (30 ml), $RuO_2 \cdot xH_2O$ (5 mg), and a 10% $NaIO_4$ solution (43 ml) were mixed and then vigorously stirred at 0 °C for 80 h. The AcOEt layer was separated and the aqueous layer was saturated with NaCl, then extracted with AcOEt (50 ml×10). Isopropyl alcohol (2 ml) was added to the combined AcOEt layers and the solution was left to stand for 2 h. The precipitated RuO_2 was filtered off and the solution was concentrated under reduced pressure. The residue was dissolved in MeOH (10 ml) and treated with diazomethane. The solution was concentrated under reduced pressure and the residual yellow oil was dissolved in $CHCl_3$ (30 ml). The solution was washed with 2% aqueous NaS_2O_3 and dried over anhydrous Na_2SO_4, then concentrated under reduced pressure to give a colorless oil. This oil was then subjected to column chromatography on silica gel (ether : hexane=1 : 1—2 : 1) to give **4** (482 mg, 58%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 3.69 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.71—3.80 (1H, m, 3-H), 4.11 (1H, t, J=8.6 Hz, 4-Ha), 4.32 (1H, dd, J=8.6, 6.6 Hz, 4-Hb), 4.87 (1H, d, J=9.5 Hz, 2-H). ^{13}C-NMR ($CDCl_3$) δ: 36.04 (d), 50.49 (t), 52.49 (q), 52.52 (q), 52.67 (q), 62.66 (d), 156.18 (s), 169.19 (s), 169.99 (s). IR ν_{max}^{neat} cm^{-1}: 1750, 1718 (C=O). MS *m/z*: 231 (M^+).

***tert*-Butyl 2-Azabicyclo[2.2.0]hex-5-ene-2-carboxylate (5)** A solution of **3** (1.00 g, 7.19 mmol) in EtOH (8.0 ml) and 2 M NaOH (8.0 ml) was refluxed for 24 h. After cooling, a solution of di-*tert*-butyl dicarbonate (1.88 g, 8.61 mmol) in ether (10 ml) was added to the reaction mixture and the whole mixture was vigorously stirred for 2 d. The ether layer was separated and the aqueous layer was extracted with ether (100 ml×3). The combined ethereal solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give an orange oil, which was then subjected to column chromatography on alumina (ether) to give **5** (746 mg, 57%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (9H, s, $C(CH_3)_3$), 3.33—3.37 (1H, s, 4-H), 3.44 (1H, d, J=8.4 Hz, 3-Ha), 3.87—3.91 (1H, m, 3-Hb), 4.72 (1H, br, 1-H), 6.43 and 6.50 (2H, br, olefinic H). ^{13}C-NMR ($CDCl_3$) δ: 28.43 (q), 37.93 (d), 49.26 (t), 50.27 (t), 64.92 (d), 65.77 (d), 79.31 (s), 140.16 (d), 140.82 (d), 143.15 (d), 156.95 (s). IR ν_{max}^{neat} cm^{-1}: 1704 (C=O), 1551 (C=C). MS *m/z*: 182 (M^++1).

Dimethyl 1-(*tert*-Butoxycarbonyl)azetidine-*cis*-2,3-dicarboxylate (6) A solution of **5** (651 mg, 3.59 mmol) in AcOEt (30 ml), $RuO_2 \cdot xH_2O$ (5 mg) and a 10% $NaIO_4$ solution (43 ml) were mixed and then vigorously stirred at 0 °C for 23 h. The AcOEt layer was separated and the aqueous layer was saturated with NaCl, then extracted with AcOEt (50 ml×5). Isopropyl alcohol (2 ml) was added to the combined AcOEt layers and the solution was left to stand for 2 h. The precipitated RuO_2 was filtered off and the solution was concentrated under reduced pressure. The residue was dissolved in MeOH (10 ml) and treated with diazomethane. The solution was concentrated under reduced pressure and the residual black oil was dissolved in $CHCl_3$ (30 ml). The solution was then washed with 2% aqueous NaS_2O_3 and dried over anhydrous Na_2SO_4, then concentrated under reduced pressure to give a black oil, which was then subjected to column chromatography on silica gel (ether : hexane=3 : 2) to give **6** (660 mg, 67%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (9H, s, $C(CH_3)_3$), 3.63—3.70 (1H, m, 3-H), 3.70 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.03 (1H, t, J=8.4 Hz, 4-Ha), 4.29 (1H, dd, J=8.4, 6.6 Hz, 4-Hb), 4.79 (1H, d, J=9.5 Hz, 2-H). ^{13}C-NMR ($CDCl_3$) δ: 28.23 (q), 35.52 (d), 49.50-51.08 (br, t), 52.30 (q), 52.52 (q), 62.16—63.16 (d), 80.66 (s), 155.12 (s), 169.49 (s), 170.17 (s). IR ν_{max}^{neat} cm^{-1}: 1754, 1712 (C=O). MS *m/z*: 273 (M^+).

Azetidine-*cis*-2,3-dicarboxylic Acid (1) Compound **6** (100 mg, 0.366 mmol) was heated in AcOH (10 ml) and 6 M HCl (10 ml) at 50 °C for 3 d. The reaction mixture was concentrated under reduced pressure. Addition of water (10 ml) to the residue and concentration of the solution were repeated three times. The residual solid was recrystallized from water to give amino acid **1** (45 mg, 85%) as colorless prisms, mp 187 °C (dec.). ^{1}H-NMR (1 M DCl) δ: 3.94 (1H, ddd, J=9.9, 9.9, 5.9 Hz, 3-H), 4.11 (1H, dd, J=11.0, 5.9 Hz, 4-Hb), 4.31 (1H, dd, J=11.0, 9.9 Hz, 4-Ha), 5.39 (1H, d, J=9.9 Hz, 2-H). ^{13}C-NMR (1 M DCl) δ: 36.20 (d), 43.12 (t), 55.81 (d), 165.33 (s), 169.38 (s). IR ν_{max}^{neat} cm^{-1}: 3100 (N–H), 1746, 1640, 1590 (C=O). MS (FAB) *m/z*: 146 (M^++1). *Anal.* Calcd for $C_5H_7NO_4$: C, 41.38; H, 4.86; N, 9.65. Found: C, 41.08; H, 4.78; N, 9.47.

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