Synthesis of α-Amino Acids Containing a Cyclopropane Ring via Cobalt-Catalyzed Carbonylation-Amidocarbonylation of Cyclopropanemethanols

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Synopsis. *N*-Acetyl-3-cyclopropylalanine and 2-acetamido-3-cyclopropylbutyric acid were prepared under cobalt-catalyzed amidocarbonylation conditions from cyclopropanemethanol and α-methylcyclopropanemethanol, respectively. The reaction has been estimated to comprise the *in situ* formation of aldehyde from alcohol by cobalt-catalyzed hydrocarbonylation followed by subsequent amidocarbonylation.

Some α-amino acids containing a cyclopropane ring are natural products.[1] Their unique structures have been of interest from a physiological viewpoint.

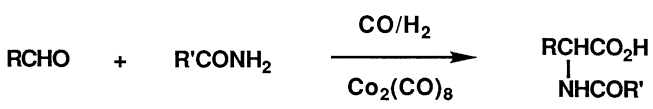
We have prepared various nonproteinogenic α-amino acids utilizing cobalt-catalyzed amidocarbonylation from amide, aldehyde, and carbon monoxide (Scheme 1).

An attempt to prepare an α-amino acid containing a cyclopropane ring from cyclopropanecarbaldehyde via amidocarbonylation was unsuccessful, giving a complex mixture. The reactive cyclopropane ring adjacent to the formyl group did not remain intact under amidocarbonylation conditions. We then turned our attention to alternative routes for the preparation of α-amino acids containing a cyclopropane ring via carbonylation-amidocarbonylation of cyclopropanemethanols.

Results and Discussion

It is well known that the cobalt-catalyzed homologation of alcohol under synthesis gas proceeds through aldehyde formation followed by hydrogenation. Benzyl alcohol having electron-releasing substituents and *t*-butyl alcohol, which easily generate a stable carbonium ion, gave homologated alcohol in good yield.[3]

Since the reaction conditions of the amidocarbonylation is the same as those of the oxo synthesis, except for the coexistence of an amide, alcohol can be carbonylated to give corresponding aldehyde, which subsequently reacts with amide and carbon monoxide to afford *N*-acyl α-amino acid under amidocarbonylation conditions. Yukawa et al. demonstrated the preparation of *N*-acetyl-*O*-methyltyrosine in 50% yield from *p*-methoxybenzyl alcohol under hydroformylation conditions in the presence of acetamide.[4] Cobalt hydridocarbonyl ($HCo(CO)_4$), which behaves as a strong acid in a polar solvent,[5] is generated *in situ* and plays an important role in giving an alkylcobalt tetracarbonyl intermediate (or a carbonium ion) from alcohol in this process. Moreover, the coexistence of an amide is essential to proceed the reactions successfully, since gas absorption could not be observed under the above-mentioned reaction conditions without acetamide, while *p*-methoxyphenylacetaldehyde was obtained in good yield using *N*,*N*-dimethylformamide in place of acetamide.[4]



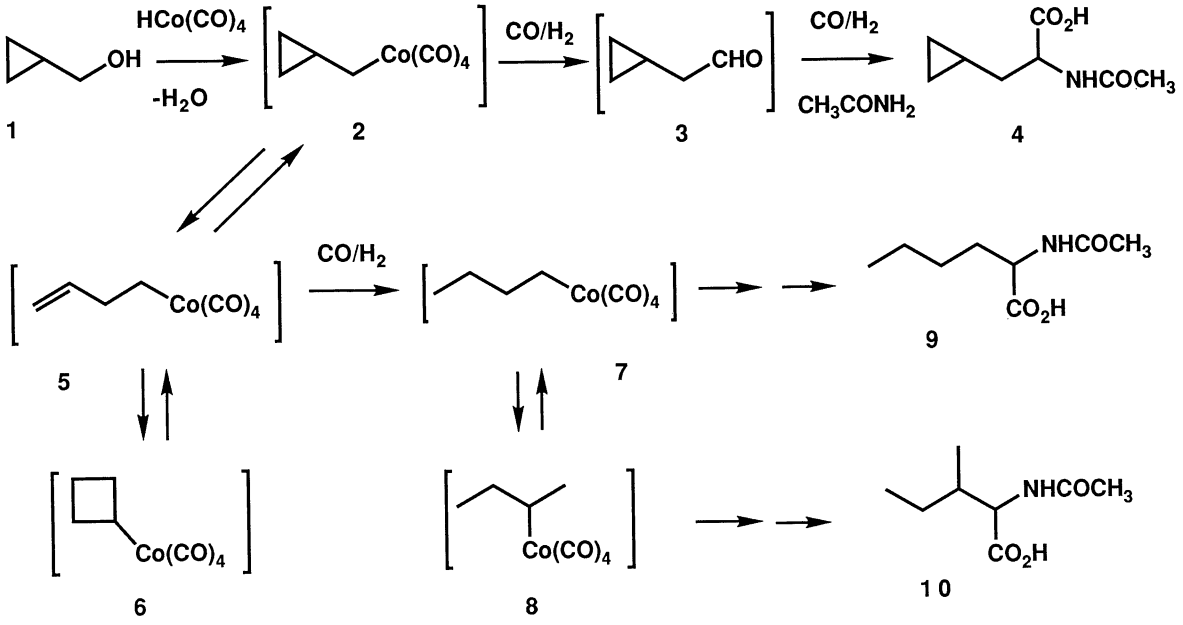
Scheme 1.

The cyclopropylmethyl cation, as well as the benzyl and *t*-butyl cations, are known to be stable carbonium ions. Whereas, the charge of the cyclopropylmethyl cation is delocalized on each of its four carbons. Namely, acidic hydrolysis of cyclopropylmethyl halide proceeds through a so-called "bicyclobutonium ion" to give cyclopropanemethanol, cyclobutanol, and 3-buten-1-ol.[6]

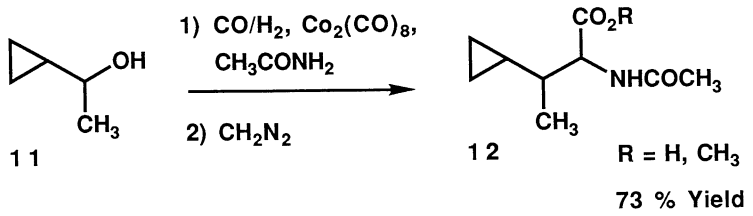
We tried to examine the use of cyclopropanemethanol (**1**) as a source for the carbonylation-amidocarbonylation. Although we had anticipated that the carbonylation-amidocarbonylation of cyclopropanemethanol (**1**) would give a mixture of *N*-acyl α-amino acids, **1** was transformed to *N*-acetyl-3-cyclopropylalanine (**4**) as the sole isolable *N*-acyl α-amino acid under amidocarbonylation conditions (see the experimental section) in ca. 8% yield. A possible mechanism for the formation of **4** is shown in Scheme 2. Changes in the reaction conditions (temperature, reaction time) as well as the addition of I_2 or CoI_2, did not increase the yield. Chloromethylcyclopropane did not give *N*-acyl α-amino acid under the same reaction conditions.

The yield of *N*-acyl α-amino acid was increased to 37% when the reaction was carried out under the following reaction conditions {$CO : H_2 = 3 : 1$ (80 atm at 25 °C), $Co_2(CO)_8$ (0.5 equiv), acetamide (2.0 equiv) at 120 °C for 18 h}. However, the product consisted of *N*-acetyl-3-cyclopropylalanine (**4**), *N*-acetylnorleucine (**9**), and *N*-acetylisoleucine (**10**) in a 1 : 1.5 : 1 ratio.

The formation of the latter two leucine derivatives can be explained as follows. Alkylcobalt tetracarbonyl intermediate (**2**) is considered to be in equilibrium with **5** and **6**. Intermediates (**7**) and (**8**) are generated by the hydrogenation of **5**, being accompanied by isomerization. Carbonylation-amidocarbonylation of **7** and **8** gives leucine derivatives, as shown in Scheme 2. Interestingly, an appreciable amount of 2-acetamido-2-cyclobutylacetic acid was not obtained, though the



Scheme 2.



Scheme 3.

possible involvement of intermediate (**6**) would not be excluded.

Next, the reaction of α-methylcyclopropanemethanol (**11**), which is known to give the 1-cyclopropylethyl cation stabilized by a hyper-conjugation of the cyclopropyl and methyl groups, was successfully revealed, giving *threo*- and erythro-2-acetamido-3-cyclopropylbutyric acid (**12**) in 73% yield. Increasing the stability of the carbonium ion (or the alkylcobalt tetracarbonyl intermediate) resulted in a selective *in situ* generation of the desired aldehyde, which is effectively incorporated into subsequent amidocarbonylation.

The usefulness of amidocarbonylation for the synthesis of nonproteinogenic α-amino acid was demonstrated by a facil preparation of *N*-acetyl derivatives of 3-cyclopropylalanine and 2-amino-3-cyclopropylbutyric acid from cyclopropanemethanols via carbonylation followed by amidocarbonylation.

Isolation of these unique α-amino acids from *Amanita echinocephala* and *A. sp.*, as well as their inhibitory activities against spore germination of *Piricularia oryzae,* were previously reported by Nozoe et al.[7]

Experimental

^{1}H NMR spectra were measured with a Varian XL 300 spectrometer and chemical shifts are given as δ ppm relative to tetramethylsilane (TMS) as an internal standard. Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrophotometer with samples as neat liquid. Mass spectra (MS) were recorded with a JEOL DX-300 instrument using the FAB technique. GC–MS was performed on an HP 5890A–5970B, with a high-performance capilary column (cross linked methyl silicone). The thin-layer chromatographic system employed silica gel Merck Art. 7515. PTLC was performed with a Whatman PLK 5F.

Reaction of Cyclopropanmethanol (1), Carbon Monoxide, and Acetamide Catalyzed by $Co_2(CO)_8$. A mixture of cyclopropanemethanol (**1**) (500 mg, 6.93 mmol), acetamide (409 mg, 6.93 mmol) and $Co_2(CO)_8$ (120 mg) in acetone (20 ml) was heated in a 100 ml stainless-steel autoclave with a 1 : 1 mixture of carbon monoxide and hydrogene (total pressure at 25 °C: 120 atm) at 100 °C for 20 h. The autoclave was then cooled to ambient temperature and depressurized. After the solvent was removed under reduced pressure, the residue was treated with 10% aqueous $NaHCO_3$ (50 ml) and an insoluble material filtered off. The filtrate was washed with AcOEt (50 ml) to remove neutral materials and acidified with concentrated HCl. The solution was extracted with AcOEt (50 ml); the extract was washed with brine, then dried over $MgSO_4$. After concentration of the solution, the residue

was esterified with ethereal diazomethane and purified by PTLC (developed with hexane : AcOEt=1 : 2, v/v) to give *N*-acetyl-3-cyclopropylalanine methyl ester (methyl ester of **4**) (105 mg, 0.57 mmol, 8.2%) as an oil.

***N*-Acetyl-3-cyclopropylalanine Methyl Ester (Methyl Ester of 4):** ^{1}H NMR (300 MHz, $CDCl_3$) δ=0.01—0.13 (2H, m, CH_2), 0.40—0.52 (2H, m, CH_2), 0.60—0.73 (1H, m, CH), 1.62—1.75 (2H, m, CH_2), 2.03 (3H, s, CH_3), 3.75 (3H, s, CH_3), 4.69 (1H, td, J=6.0 and 7.8 Hz, CH), 6.25 (1H, br. d, J=6.0 Hz, NH); IR (neat) 3280, 3060, 3000, 2950, 1740, 1650, 1540, 1435, 1375, 1205, 1160, 1008 cm^{-1}; GC–MS m/z 153 (M^+ −32), 142 (M^+ −43), 126 (M^+ −59). High mass (FAB) m/z Calcd for $C_9H_{15}N_1O_3$+H: 186.1130. Found: 186.1123; R_f 0.63 ($CHCl_3$: MeOH=10 : 1, v/v on silica gel).

Methyl 2-Acetamido-3-cyclopropylbutyrate (Methyl Ester of 12): ^{1}H NMR (300 MHz, $CDCl_3$) δ=0.01—0.22 (2H, m, CH_2), 0.42—0.51 (2H, m, CH_2), 0.57—0.63 (1H, m, CH), 1.01 (3H, d, J=6.9 Hz, CH_3), 1.15—1.38 (1H, m, CH), 2.04 and 2.05 (3H, s, CH_3), 3.73 and 3.74 (3H, s, CH_3), 4.71 (1H, m, CH), 6.10 and 6.19 (1H, d, J=6.9 Hz, NH); IR (neat) 3300, 3060, 2990, 2950, 1740, 1650, 1435, 1430, 1370, 1205, 1145, 1005 cm^{-1}; GC–MS m/z 167 (M^+ −32), 156 (M^+ −43), 140 (M^+ −59). High mass (FAB) m/z Calcd for $C_{10}H_{17}N_1O_3$+H: 200.1287. Found: 200.1300; R_f 0.70 ($CHCl_3$: MeOH=10 : 1, v/v on silica gel).

***N*-Acetylnorleucine Methyl Ester (Methyl Ester of 9):** ^{1}H NMR (300 MHz, $CDCl_3$) δ=0.89 (3H, t, J=6.9 Hz, CH_3), 1.26—1.35 (4H, m, CH_2), 1.58—1.85 (2H, m, CH_2), 2.03 (3H, s, CH_3), 3.75 (3H, s, CH_3), 4.60 (1H, td, J=7.2 and 6.0 Hz, CH), 6.03 (1H, br. d, J=3.9 Hz, NH); IR (neat) 2960, 1745, 1660, 1540, 1440, 1380, 1220, 1160 cm^{-1}. GC–MS m/z 187 (M^+), 155 (M^+ −32), 140 (M^+ −43), 128 (M^+ =59).

***N*-Acetylisoleucine Methyl Ester (Methyl Ester of 10):** ^{1}H NMR (300 MHz, $CDCl_3$) δ=0.85—0.95 (6H, m, CH_3), 1.10—1.25 (1H, m, CH_2), 1.38—1.50 (1H, m, CH_2), 1.80—1.92 (1H, m, CH), 2.03 (3H, s, CH_3), 3.74 (3H, s, CH_3), 4.60 (0.5H, dd, J=9.0 and 5.4 Hz, CH), 4.72 (0.5H, dd, J=9.0 and 4.2 Hz, CH), 6.06 (1H, br. d, J=8.1 Hz, NH); IR (neat) 2960, 1740, 1650, 1540, 1435, 1380, 1205, 1150 cm^{-1}; GC–MS m/z 155 (M^+ −32), 144 (M^+ −43), 128 (M^+ −59).

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