Synthesis of Proline and 2-Piperidinecarboxylic Acid via Cobalt-Catalyzed Isomerization-Carbonylation of *N*-Acyl Unsaturated Cyclic Amines

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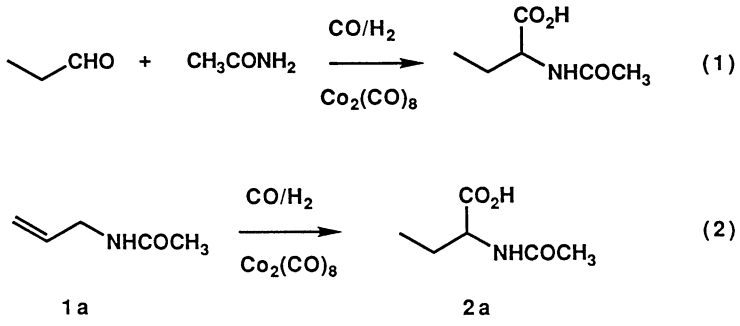
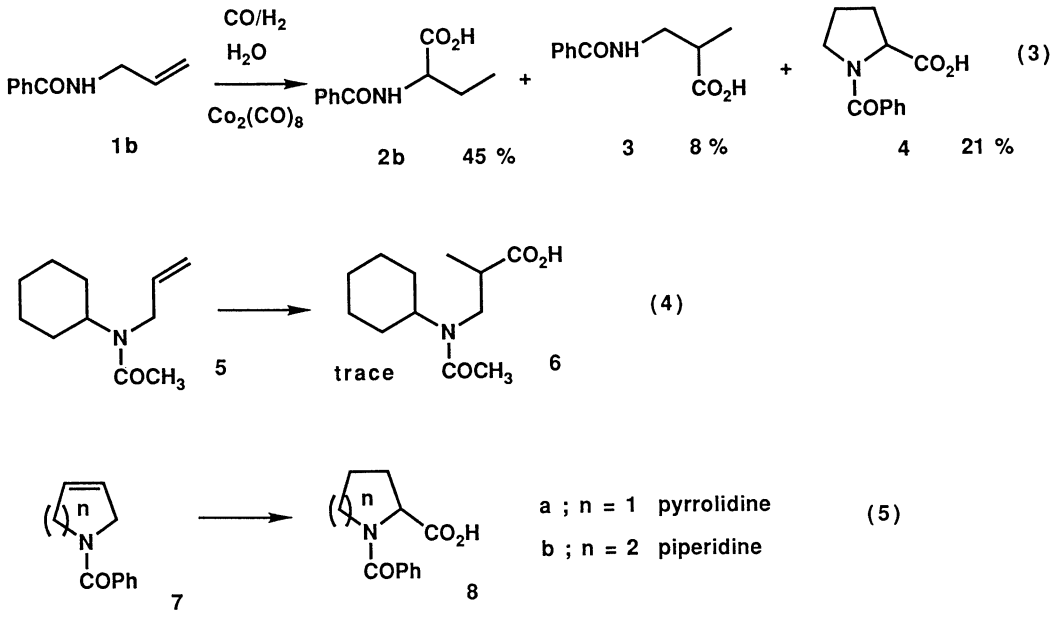
N-Acyl derivatives of proline and 2-piperidinecarboxylic acid (pipecolic acid) were synthesized in moderate yield from *N*-acyl unsaturated cyclic amines through cobalt-catalyzed isomerization-carboxylation under hydroformylation conditions in the presence of H_2O. A possible mechanism for the process is discussed which is related to that of the amidocarbonylation (cobalt-catalyzed formation of *N*-acyl α-amino acid from aldehyde, amide and carbon monoxide).

The cobalt-catalyzed formation of amido carboxylic acid (tentatively designated as amidocarbonylation hereafter) has been developed by Wakamatsu et al. as a useful method for the synthesis of *N*-acyl α-amino acid from aldehyde, amide and carbon monoxide (Eq. 1).[1] The remarkable features of the reaction are its highly regioselective α-carbonylation and hydrolysis, rather than the hydrogenolysis of the acyl complex under hydroformylation conditions.

On the other hand, Sato has reported that *N*-acetylallylamine (**1a**) uniquely reacts with carbon monoxide to give 2-acetamidobutyric acid (**2a**) in 29%



Scheme 1.



Scheme 2.

yield under hydroformylation conditions (Eq. 2).[2]

We have been interested in the fact that the product (**2a**) corresponds to the amidocarbonylation product of propionaldehyde and acetamide. The reaction can be explained by a facile migration of the cobalt carbonyl moiety from the β- or γ-position to the α-position of the acylamino group, followed by CO insertion. The resulting acyltetracarbonylcobalt intermediate [$Co(RCO)(CO)_4$] with the acylamino group on the α-carbon specifically undergoes hydrolytic cleavage to give **2a**.

Previously, the reaction of *N*-benzoylallylamine (**1b**) under hydroformylation conditions by the addition of one mole equivalent of H_2O was reinvestigated. The reaction was complicated, giving 2-benzamidobutyric acid (**2b**) and 3-benzamido-2-methylpropionic acid (**3**) as well as *N*-benzoylproline (**4**) (Eq. 3).[3] The formation of *N*-benzoylproline (**4**) can be explained by hydroformylation followed by subsequent intramolecular amidocarbonylation.

Though Magnus and co-workers examined the reaction of *N*-acetyl-*N*-cyclohexylallylamine (**5**) under hydroformylation conditions, they obtained a β-carboxylation product **6** in low yield, and could not obtain an α-carboxylation product (Eq.4).[4]

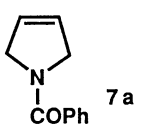
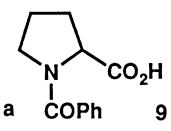
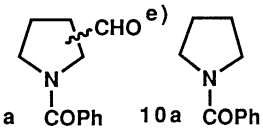
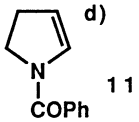
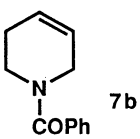
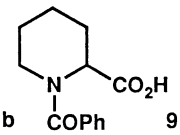
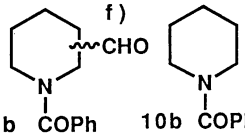
We then intended to examine the cobalt-catalyzed isomerization-hydrocarboxylation of *N*-acyl-β,γ-unsaturated cyclic amine (**7**) to obtain *N*-acylproline (**8a**) and *N*-acyl-2-piperidinecarboxylic acid (*N*-acylpipecolic acid) (**8b**) (Eq.5).

Results and Discussion

We found that the cobalt-catalyzed isomerization-hydrocarboxylation of *N*-benzoyl-β,γ-unsaturated cyclic amine (**7**) under hydroformylation conditions with the addition of two equivalents of H_2O (initial pressure at 25 °C: CO, 60 atm; H_2, 60 atm) at 100 °C for 24 h proceeded smoothly to give *N*-benzoyl cyclic α-amino acid (**8**) in moderate yield.

As shown in Table 1, *N*-benzoyl cyclic α-amino acids (**8**), as well as the isomerization-hydroformylation products (**9**) and hydrogenation products (**10**), were obtained as major products. In the case of cyclic

Table 1. Synthesis of Cyclic α-Amino Acids

Run	Substrate	Catalyst	Products, yield[a]/%		
	 7a		 8a	 9a	10a
1		$Co_2(CO)_8$	54	6	16
2		$Co_2(CO)_8$ / $PdCl_2(PPh_3)_2$ b)	47	22	6
3		$Co_2(CO)_8$ / CH_3CONH_2 c)	44	18	15
4	 d) 11	$Co_2(CO)_8$	32	47	19
	 7b		 8b	 9b	10b
5		$Co_2(CO)_8$	61	16	6
6		$Co_2(CO)_8$ / $PdCl_2(PPh_3)_2$ b)	75	16	3
7		$Co_2(CO)_8$ / $[RhH(CO)(PPh_3)_3]$ b)	55	21	6

a) Carboxylic acids were isolated as methyl esters. Neutral materials were analyzed by GC-MS. b) 0.25 equiv to $Co_2(CO)_8$. c) 5 equiv to $Co_2(CO)_8$. d) 100 °C, 2 h. e) α-Isomer>90%. f) α-: β- or γ-Isomer=1 : 1.

substrates, the only detectable hydrocarboxylation product was an α-carboxylation isomer, and the corresponding β- or γ-isomer was not obtained. It is postulated that the acylamino group of an (α-amidoalkyl)acylcobalt intermediate participated in the hydrolysis of the acyl-cobalt bond in this intermediate (Scheme 3), while the hydrolysis of sterically restricted (β- or γ-amidoalkyl)acylcobalt intermediates is thought to be difficult to give β- or γ-carboxylation products.

It is interesting that since the hydroformylation also proceeded after isomerization, the α-formyl product (**9a**) was obtained as a major isomer in the reaction of *N*-benzoyl-3-pyrroline (**7a**).

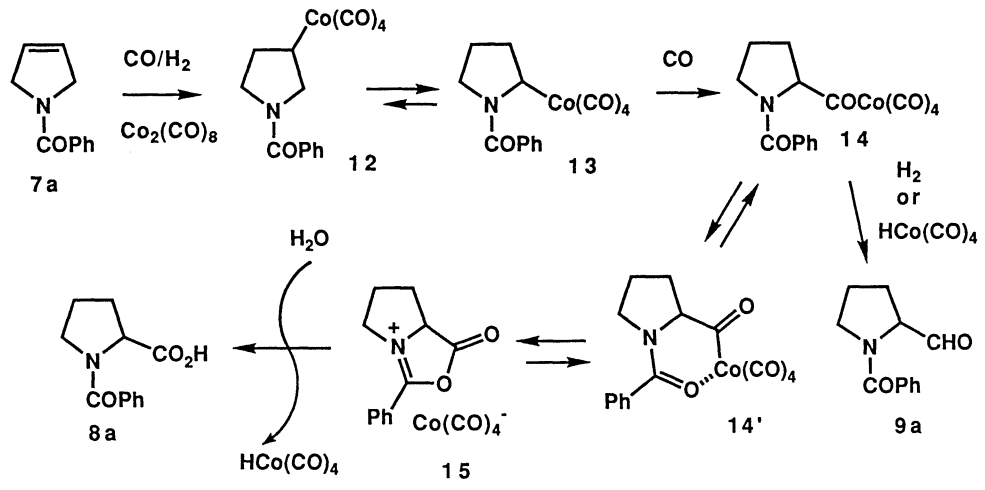
Isomerization of the alkylcobalt intermediate, a key step in this reaction, is thought to be promoted by stabilization to the (α-amidoalkyl)cobalt intermediate (similar to *N*-acyliminium cation). To accelerate isomerization, $PdCl_2(PPh_3)_2$ and $[RhH(CO)(PPh_3)_3]$, which were used by Stille and co-workers as isomerization catalysts of the unsaturated amide and imide,[5a] were added as a co-catalyst. However, the effect of the co-catalyst was not remarkable; only the addition of $PdCl_2(PPh_3)_2$ slightly increased the yield of *N*-benzoyl-2-piperidinecarboxylic acid (Run 6). Evans and co-workers reported a $PdCl_2(PPh_3)_2$ catalyzed hydroesterification [hydro(methoxycarbonyl)ation] of *N*-acetyl-1,2,3,6-tetrahydropyridine.[6] They obtained methyl *N*-acetyl-2-piperidinecarboxylate only in 12% yield, together with regioisomers (major products), *N*-acetyl-2-methoxypiperidine, and *N*-acetyl-1,2,3,4-tetrahydropyridine (minor products). These results indicate that the alkylcobalt intermediate is more liable to isomerize relative to the alkylpalladium intermediate.

The coexistence of an amide sometimes decreases the regioselectivity of the hydroformylation step in the hydroformylation-amidocarbonylation of olefins. This fact may be explained by the exchanged regioselectivity of a cobalt hydridocarbonyl catalyst in the presence of amide.[7] Though the reaction was then tried with the addition of acetamide, the reaction was not affected by the addition of acetamide (Run 3).

The reaction of previously isomerized *N*-benzoyl-2-pyrroline (**11**)[5a] under milder reaction conditions also gave the same products as did *N*-benzoyl-3-pyrroline (**7a**) in different product ratios (Run 4). It is unclear why the hydroformylation product (**9a**) was produced predominantly when **11** was used.

A possible mechanism of this reaction is shown in Scheme 3. (*N*-Benzoyl-3-pyrrolidinyl)tetracarbonylcobalt (**12**) isomerizes to the more stable (*N*-benzoyl-2-pyrrolidinyl)tetracarbonylcobalt (**13**), which then produces the (*N*-benzoyl-2-pyrrolidinoyl)tetracarbonylcobalt (**14**) through the insertion of carbon monoxide. The acyl complex (**14**) then undergoes a hydrolytic cleavage (**14**→**8a**), rather than hydrogenolysis (**14**→**9a**), to give *N*-acyl cyclic α-amino acid in a manner similar to that of amidocarbonylation. We have already proposed that cyclization to the oxazolone-like ion pair (**15**), via an intramolecular nucleophilic attack of the oxygen atom if the acylamino moiety is adjacent to the acylcobalt complex, may promote a solvolytic cleavage of the acyl-cobalt bond in the amidocarbonylation.[8] As shown in the Table 1, though the hydrolytic cleavage is the preferred route to hydrogenolysis in this process, the amount of the hydroformylation product (**9a**) is not negligible. At present, it is not clear why hydrogenolysis proceeds to such a degree.

We have already presented the preparation of *N*-acyl cyclic α-amino acid, such as proline and 2-piperidinecarboxylic acid, via the intramolecular amidocarbonylation of ω-(acylamino)alkanals[9] or cobalt-catalyzed carbonylation of *N*-acyl α-alkoxyalkylamines.[8] Another example regarding the preparation of *N*-acyl cyclic α-amino acid via the cobalt-catalyzed carbonylation was developed here.



Scheme 3.

Stille and co-workers achieved proline derivative synthesis from *N*-*t*-butoxycarbonyl-3-pyrroline, which is a similar starting material to our's, through the subsequent isomerization, hydroformylation and oxidation.[5] We achieved a similar process by one-pot synthesis utilizing cobalt-catalyzed carbonylation.

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 by using the FAB technique. GC-MS was performed on a HP 5890A-5970B with a high-performance capillary column (cross-linked methyl silicone). The thin-layer chromatographic system employed silica gel (Merck Art. 7515). PTLC was performed with a Whatman PLK 5F.

N-Benzoyl-3-pyrroline (**7a**) and *N*-benzoyl-1,2,3,6-tetrahydropyridine (**7b**) were prepared by the reaction of amines and benzoyl chloride.

***N*-Benzoyl-3-pyrroline (7a):** ^{1}H NMR (300MHz, $CDCl_3$) δ=4.18—4.23 (2H, m, CH_2), 4.44—4.49 (2H, m, CH_2), 5.72—5.78 (1H, m, -CH=), 5.89—5.94 (1H, m, -CH=), 7.38—7.55 (5H, m, aromatic H); IR (neat) 3050, 2850, 1635, 1605, 1570, 1410 cm^{-1}; GC-MS *m*/*z* 173 (M^+).

***N*-Benzoyl-1,2,3,6-tetrahydropyridine (7b):** ^{1}H NMR (300MHz, $CDCl_3$) δ=2.25 (2H, br. s, CH_2), 3.46, 3.86, and 4.20 (4H, br. s, CH_2), 5.50—5.90 (2H, m, -CH=), 7.41 (5H, br. s, aromatic H); IR (neat) 3050, 2940, 2850, 1700, 1630, 1580, 1435, 1290, 1260 cm^{-1}; GC-MS *m*/*z* 187 (M^+).

N-Benzoyl-2-pyrroline (**11**) was prepared by isomerization of *N*-benzoyl-3-pyrroline (**7a**) with $[RhH(CO)(PPh_3)_3]$.[5a] ^{1}H NMR (300MHz, $CDCl_3$) δ=2.67—2.76 (2H, m, CH_2), 4.03 (2H, t, *J*=9.0 Hz, CH_2), 5.15—5.23 (1H, m, -CH=), 6.42—6.67 (1H, m, -CH=), 7.33—7.55 (5H, m, aromatic H); IR (neat) 1610, 1570, 1410 cm^{-1}; GC-MS *m*/*z* 173 (M^+).

Isomerization-Carboxylation of *N*-Acyl Unsaturated Cyclic Amines (7). A typical procedure is described for the reaction of *N*-benzoyl-3-pyrroline (**7a**) and carbon monoxide catalyzed by $Co_2(CO)_8$.

N-Benzoyl-3-pyrroline (**7a**) (606 mg, 3.5 mmol), $Co_2(CO)_8$ (100 mg, 0.29 mmol), and H_2O (0.13 ml, 7.2 mmol) in THF (20 ml) were heated in a 100 ml stainless-steel autoclave with a 1:1 mixture of carbon monoxide and hydrogen (total pressure 120 atom, measured at room temperature) at 110 °C for 24 h. The autoclave was then cooled to ambient temperature and carbon monoxide and hydrogen were purged out. After the solvent was removed under reduced pressure, the residue was dissolved in AcOEt (50 ml) and the insoluble material filtered off. The filtrate was extracted with 10% aqueous $NaHCO_3$ (50 ml) and brine. The organic phase was dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue analyzed by GC-MS; it was then purified by PTLC (hexane : AcOEt=1 : 2, v/v) to give *N*-benzoyl-2-pyrrolidinecarbaldehyde (**9a**) (44 mg, 0.22 mmol, 6.3%) and *N*-benzoylpyrrolidine (**10a**) (98 mg, 0.56 mmol, 16.0%) as major products. The aqueous $NaHCO_3$ extract was acidified with concentrated HCl and extracted with AcOEt (50 ml). The organic layer was washed with brine and dried over $MgSO_4$. After concentration, the residue was esterified with etherial CH_2N_2 and purified by PTLC (hexane : AcOEt=1 : 2, v/v) to give *N*-benzoylproline methyl ester (methyl ester of **8a**) (443 mg, 1.90 mmol, 54.3%) as an oil.

***N*-Benzoylproline Methyl Ester (Methyl Ester of 8a):** ^{1}H NMR (300MHz, $CDCl_3$) δ=1.50—2.30 (4H, m, CH_2), 3.45—3.55 (2H, m, CH_2), 3.75 (3H, s, CH_3), 4.66 (1H, dd, *J*=5.1 and 8.3 Hz, CH), 7.30—7.58 (5H, m, aromatic H); IR (neat) 2950, 2880, 1740, 1630, 1420, 1280, 1200, 1180 cm^{-1}; GC-MS *m*/*z* 233 (M^+), 174 (M^+−59); High mass (FAB) *m*/*z* Calcd for $C_{13}H_{15}N_1O_3$+H: 234.1130. Found: 234.1136.

***N*-Benzoyl-2-pyrrolidinecarbaldehyde (9a):** ^{1}H NMR (300MHz, $CDCl_3$) δ=2.30—2.85 (4H, m, CH_2), 3.50—3.70 (2H, m, CH_2), 4.65—4.72 (1H, m, CH), 7.35—7.63 (5H, m, aromatic H), 9.68 (1H, s, CHO); IR (neat) 1730, 1625, 1580, 1420 cm^{-1}; GC-MS *m*/*z* 174 (M^+−29).

***N*-Benzoylpyrrolidine (10a):** ^{1}H NNR (300MHz, $CDCl_3$) δ=1.87 (2H, q, *J*=6.6 Hz, CH_2), 1.94 (2H, q, *J*=6.6 Hz, CH_2), 3.42 (2H, t, *J*=6.6 Hz, CH_2), 3.65 (2H, t, *J*=6.6 Hz, CH_2), 7.35—7.55 (5H, m, aromatic H); IR (neat) 3050, 2970, 2890, 1620, 1575, 1410, 1340 cm^{-1}; GC-MS *m*/*z* 175 (M^+).

Methyl *N*-Benzoyl-2-piperidinecarboxylate (Methyl Ester of 8b): ^{1}H NMR (300MHz, $CDCl_3$) δ=1.35—1.85 (4H, m, CH_2), 2.20 (0.5H, br. d, CH_2), 2.35 (1H, br. d, CH_2), 2.85 (0.5H, m, CH_2), 3.25 (1H, br. t, CH_2), 3.65 (1H, br. d, CH_2), 3.78 (3H, br. s, CH_3), 4.45—4.70 (0.5H, m, CH), 5.50 (0.5H, br. s, CH), 7.40 (5H, br. s, aromatic H); IR (neat) 2950, 2860, 1740, 1640, 1420, 1280, 1210 cm^{-1}; GC-MS *m*/*z* 247 (M^+); High mass (FAB) *m*/*z* Calcd for $C_{14}H_{17}N_1O_3$+H: 248.1287. Found 248.1278.

Mixture of *N*-Benzoyl-2-piperidinecarbaldehyde and Regioisomer(s) (9b): ^{1}H NMR (300MHz, $CDCl_3$) δ=9.50 (s, CHO); IR (neat) 1730 cm^{-1}; GC-MS *m*/*z* 217 (M^+), 216 (M^+−1), 188 (M^+−29).

***N*-Benzoylpiperidine (10b):** ^{1}H NMR (300MHz, $CDCl_3$) δ=1.45—1.80 (6H, m, CH_2), 3.34 (2H, br. s, CH_2), 3.70 (2H, br. s, CH_2), 7.38 (5H, br. s, aromatic H); IR (neat) 2940, 2850, 1630, 1575, 1440, 1275 cm^{-1}; GC-MS *m*/*z* 189 (M^+), 188 (M^+−1).

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